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(54) Title: SELF-EMULSIFYING DRUG DELIVERY SYSTEMS FOR HYDROPHOBIC THERAPEUTIC COMPOUNDS

(57) Abstract: A novel self-emulsifying drug delivery system (SEDDS) useful for the administration of a water-insoluble drug to a patient is disclosed. The SEDDS comprises a hydrophilic surfactant with hydrophilic-lipophilie balance (HLB) value greater than 10, a digestible oil comprised of medium chain fatty acids esters of propylene glycol, and a non-aqueous protic solvent. Optionally, a soluble chelating agent and antioxidant may be added to enhance the stability of the phenolic antioxidant drug.

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SELF-EMULSIFYING DRUG DELIVERY SYSTEMS FOR HYDROPHOBIC THERAPEUTIC COMPOUNDS

RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Patent Application Nos. 60/511,652, filed October 17, 2003 and 60/536,989, filed January 20, 2004, both of which are incorporated by reference in their entireties.

FIELD OF THE INVENTION

The present invention is directed to self-emulsifying drug delivery systems, particularly those adapted to deliver hydrophobic therapeutic compounds, including phenolic antioxidants, as well as methods for use of such compositions.

BACKGROUND OF THE INVENTION

The use of many pharmaceutically active compounds is severely limited due to low aqueous solubility. These compounds, often described as "lipophilic" or "hydrophobic," do not dissolve well in water, and may even form a separate physical phase in aqueous solutions. Steroidal drugs (cortisone, danazol, spironolactone), taxol, and amphotericin B are examples of hydrophobic drugs. Their low solubility in the aqueous environment of the gastrointestinal tract results in poor and inconsistent bioavailability and hampers the development of pharmaceutical products.

Phenolic antioxidants, *e.g.*, 2,6-di-alkyl-4-silyl-phenols, are another example of hydrophobic pharmaceutically active compounds. These compounds are thought to inhibit low density lipoprotein (LDL) peroxidation, to inhibit formation or growth of atherosclerotic lesions or plaques and to lower plasma cholesterol concentrations (see, for example, U.S. Patent No. 5,155,250; U.S. Patent No. 5,677,291; and U.S. Patent No. 5,962,435; incorporated by reference).

Considerations of cost, safety and patient compliance motivate the search for effective oral formulations of hydrophobic therapeutic compounds. Conventional oral formulations of hydrophobic pharmaceutical drugs, while allowing the administration of higher concentrations of the compounds in a unit dose, and satisfying the concerns of expense, safety and patient convenience present additional problems. For example,

orally administered hydrophobic drugs afford a limited fraction of the water-soluble form available for absorption, or may accumulate in the gastrointestinal tract without being transported into the general circulation. In addition, even if the drug does enter the circulation, the drug may undergo a "first pass metabolism" upon passage through the liver, in which the liver degrades and removes a significant fraction of the drug from the circulation. The first pass effect may vary among individuals. As a result, this is another reason why orally administered hydrophobic drugs often exhibit low and variable bioavailability.

One approach to increase the bioavailability of an insoluble, hydrophobic drug is to administer the drug in the form of an oil-in-water emulsion. In such an emulsion, the drug is dissolved in an oil phase which is finely dispersed in an aqueous phase. The drug in the resulting droplets of oil in water is absorbed more readily in the small intestine as compared to the drug in a non-emulsified oil. However, emulsion dosage forms are typically thermodynamically unstable, and can separate into distinct oil and water phases if the oil concentration is too high. Consequently, only a limited amount of oil can be added to form a practically usable emulsion. The limited amount of oil in turn limits the amount of the hydrophobic drug that can be added into the formulation and, consequently, the potency or concentration of the resulting formulation.

To overcome the limitations of aqueous and emulsion dosage forms for the administration of hydrophobic drugs, some drugs have been formulated in vehicles that are not themselves emulsions, but which readily form an oil-in-water emulsion when gently mixed in water or aqueous media. These compositions are termed self-emulsifying drug delivery systems (SEDDS). SEDDS are non-aqueous mixtures of oils, other non-aqueous solvents and surfactants, often isotropic, which spontaneously form an emulsion upon introduction into an aqueous medium under conditions of gentle agitation similar to those encountered in the gastrointestinal tract (Pouton, CW, *Adv. Drug Delivery Rev.* 1997 25:47-58). Because SEDDS contain no aqueous components, a high concentration of a hydrophobic drug may be incorporated into the vehicle. When a SEDDS containing a hydrophobic pharmaceutical drug is orally ingested by a patient, the resulting composition disperses in the gut to form a fine emulsion that does not separate into an aqueous phase and an oil phase. Likewise, a

SEDDS formulation can be finely dispersed in a beverage that is consumed by a patient. In this manner the drug remains in solution in the gut, and can provide improved bioavailability and/or a more consistent absorption than conventional oral solid- or simple solution-based drug formulations.

A wide variety of SEDDS formulations have been tested for use as drug delivery vehicles. Liu *et al.* described a SEDDS composition for the lipophilic drug fenofibrate that comprised acetylated monoglycerides and various surfactants (Liu, R. *et al.*, *AAPS Pharm. Sci. Suppl.*, 1999, 3281). The bioavailability of the drug in the SEDDS formulation was increased relative to that of the same drug in a commercially available preparation. A SEDDS comprising a medium-chain triglyceride oil (Neobee® M5) and a nonionic surfactant (TAGAT® TO) was prepared for oral administration of an investigational lipophilic compound (WIN 54954) (Charman, S.A. *et al.*, *Pharmaceutical Res.*, 1992, 9(1):87-93). The drug was formulated in SEDDS soft gelatin capsules and as an oil-in-water intravenous formulation, and compared to the same drug administered in a polyethylene glycol (PEG) solution soft gelatin capsule. Compared to the PEG capsule, the drug plasma concentration vs. time profile for the intravenous formulation and the SEDDS capsule were more consistent.

Because of its importance as an immunosuppressant, a number of different compositions for delivery of the insoluble drug cyclosporin have been developed. WO 97/48410 describes a composition for delivery of cyclosporin in a soft capsule that comprises a surfactant having an HLB (hydrophilic-lipophilic balance) between 8 and 17; a mixture of an esterified compound of fatty acid and primary alcohol, medium chain fatty acid triglyceride and fatty acid monoglyceride as an oil component; and one or both of polyethylene glycol or propylene carbonate. This composition was reported to provide greater bioavailability and more consistent blood levels than prior art cyclosporin formulations. WO 99/20296, WO 97/07787 and WO 97/35603 describe cyclosporin A formulations that contain a lower alkanol (i.e., 2-3 carbon atoms) in combination with at least one non-ionic surfactant, particularly a polyoxyalkylene surfactant. The formulations may also contain cosolvents that comprise fatty acids and diols. WO 99/44584 describes a microemulsion preconcentrate useful for administration of an insoluble active agent, such as

cyclosporin. The preconcentrate comprises an active agent solvent, chiefly fatty acid esters of various forms in which the insoluble agent has a solubility between about 20 to 50%; a lipophilic component; and a surfactant. The lipophilic component is described as preferably a medium chain triglyceride, mixed mono-di- and triglycerides, or transesterified ethoxylated vegetable oils. EP 0711550 A1 discloses a microemulsion concentrate containing cyclosporin that comprises an oil component, a surfactant having an HLB value between 10 and 17, and dimethylisosorbide as a cosurfactant. The oil component more specifically comprised one or more of an esterified compound of fatty acid and a primary alcohol, a medium chain triglyceride, and a monoglyceride.

There is a need for a vehicle for the administration of hydrophobic and lipophilic drugs in a safe, effective and reproducible manner.

SUMMARY OF THE INVENTION

The present invention is directed to a novel self-emulsifying drug delivery system (SEDDS) suitable for use in the administration of hydrophobic therapeutic compounds, for example, phenolic antioxidants, to patients. In accordance with one aspect of the invention, a vehicle system for hydrophobic or lipophilic phenolic antioxidants includes a digestible oil comprising a propylene glycol ester of one or more medium chain fatty acids; a pharmaceutically acceptable hydrophilic surfactant having an HLB value greater than 10 and being capable of dispersing the oil into water or aqueous media; a pharmaceutically acceptable non-aqueous protic solvent capable of forming an isotropic mixture with the oil and surfactant; optionally a pharmaceutically acceptable chelating agent soluble in a non-aqueous system; and optionally a pharmaceutically acceptable antioxidant soluble in a non-aqueous system.

In another aspect of the invention, a pharmaceutical composition includes a phenolic antioxidant and a vehicle system that includes a digestible oil comprising a propylene glycol ester of one or more medium chain fatty acids; a pharmaceutically acceptable hydrophilic surfactant having an HLB value greater than 10 and being capable of dispersing the oil into water or aqueous media; a pharmaceutically acceptable non-aqueous protic solvent capable of forming an isotropic mixture with the oil and surfactant; optionally a pharmaceutically acceptable chelating agent

soluble in a non-aqueous system; and optionally a pharmaceutically acceptable antioxidant soluble in a non-aqueous system.

In another aspect of the invention, a pharmaceutical composition useful in the administration of a hydrophobic or lipophilic drug comprises a hydrophilic surfactant with a hydrophilic-lipophilic balance value greater than 10; a digestible oil consisting essentially of one or more medium chain fatty acid esters of propylene glycol; and a non-aqueous protic solvent.

In another aspect of the invention, a pharmaceutical composition useful in the administration of a hydrophobic or lipophilic drug comprises polyoxyl 40 hydrogenated castor oil at a concentration between 5 and 80% (w/v); propylene glycol dicaprylate/dicaprate at a concentration between 5 and 80% (w/v); dehydrated ethanol at a concentration between 5 and 50%(w/v); optionally butylated hydroxytoluene at a concentration of between 0.01 and 10%(w/v); and optionally citric acid that is present at a concentration between 0.01 and 10% (w/v).

In another aspect of the invention, a method for treating a patient in need of a vascular protective treatment includes administering to the patient a therapeutically effective amount of an phenolic antioxidant in a pharmaceutically acceptable carrier comprising a hydrophilic surfactant with a hydrophilic-lipophilic balance value greater than 10; a digestible oil consisting essentially of one or more medium chain fatty acid esters of propylene glycol; and a non-aqueous protic solvent.

In another aspect of the invention, a method for treating a patient in need of a vascular protective treatment includes administering to the patient an effective amount of an effective phenolic antioxidant in a pharmaceutically acceptable carrier comprising polyoxyl 40 hydrogenated castor oil at a concentration between 5 and 80% (w/v); propylene glycol dicaprylate/dicaprate at a concentration between 5 and 80% (w/v); dehydrated ethanol at a concentration between 5 and 50%(w/v); optionally butylated hydroxytoluene at a concentration of between 0.01 and 10%(w/v); and optionally citric acid at a concentration between 0.01 and 10% (w/v).

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

A novel self-emulsifying drug delivery system (SEDDS) has been developed. The SEDDS of the invention generally includes an effective surfactant, a digestible

oil comprised of one or more medium chain fatty acids esters of propylene glycol, and an effective non-aqueous protic solvent. Optionally, a chelating agent and/or a soluble antioxidant may beincluded in the SEDDS of the invention. The SEDDS of the invention may be used for any effective purpose, including, for example, for the administration of hydrophobic drugs to a patient.

A SEDDS composition containing propylene glycol dicaprylate/dicaprate was discovered to unexpectedly afford a significantly higher oral bioavailability of phenolic antioxidant drugs in monkeys as compared to a SEDDS prepared with triglycerides bearing the same medium chain fatty acids (See Table 4). While not wishing to be bound by theory, a possible explanation for this finding is that triglycerides may be hydrolyzed by pancreatic lipases to 2-monoglycerides which solubilize the drug in the gut and are absorbed and re-esterified to triglycerides for transport through the lymphatic system. Propylene glycol diesters are similarly hydrolyzed to the drug-solubilizing 2-monoester form which, due to its higher lipophilicity, may be absorbed more readily than 2-monoglycerides produced from the triglycerides.

Unless otherwise required by the context, as used herein the term "surfactant" refers to a group of surface-active amphiphilic molecules that reduce surface tension of liquids, or reduce interfacial tension between two liquids or a liquid and a solid.

Unless otherwise required by the context, as used herein the term "medium chain fatty acid" refers to fatty acyl chains of between 6 and 14 carbons in length, more preferably between 8 and 12 carbons in length.

Unless otherwise required by the context, as used herein the term "long chain fatty acid" refers to fatty acyl chains greater than 14 carbons in length.

Unless otherwise required by the context, as used herein the term "short chain fatty acid" refers to fatty acyl chains less than 6 carbons in length.

Unless otherwise required by the context, as used herein the term "pharmaceutically acceptable" means that drugs, medicaments or inert ingredients which the term describes are generally suitable for *in vivo* use in humans and animals without producing unacceptable levels of morbidity, mortality, toxicity, irritation, immune response, and the like.

Unless otherwise required by the context, as used herein the term "hydrophilic-lipophilic balance" value, or HLB value, refers to an empirically-derived formula used to describe compounds, especially surfactants, based on their hydrophilicity. It is generally accepted that those compounds with an HLB value of less than 10 are considered lipophilic, while those with an HLB value of greater than 10 are considered hydrophilic.

Unless otherwise required by the context, as used herein the term "digestible oil" refers to an oil that can be safely digested and metabolized by a living human and animal.

Unless otherwise required by the context, as used herein the term "emulsion" refers to a thermodynamically unstable colloidal dispersion of two immiscible liquids in the form of droplets whose diameters are generally in the range of 0.1 to 3 microns in diameter.

Unless otherwise required by the context, as used herein the term "microemulsion" refers to a thermodynamically stable, isotropically clear dispersion of two immiscible liquids, stabilized by an interfacial film of surfactant molecules. Microemulsions typically have droplets whose diameters are 100 nm or less. The dispersion comprises two distinct phases, and is optically opaque unless the two phases are matched in refractive index.

Unless otherwise required by the context, as used herein the term "antioxidant" refers to any chemical compound or composition that has the ability to prevent or reduce oxidation.

Unless otherwise required by the context, as used herein the term "vascular protective properties" includes those properties that inhibit processes that damage, destroy, or reduce the effectiveness/function of blood vessels, or prevent worsening of existing damage or disfunction. Examples of such vascular protective properties include lowering blood plasma cholesterol levels, inhibiting LDL peroxidation, inhibiting VCAM expression or action in the vasculature, and inhibiting the formation or growth of atherosclerotic lesions or plaques. An amount adequate to prevent worsening, reduce or inhibit such processes that damage, destroy, or reduce the effectiveness of blood vessels is an "effective amount."

Any effective surfactant, or effective combinations thereof, may be used in accordance with the present invention. Acceptable surfactants for use in the SEDDS compositions of the present invention include pharmaceutically acceptable surfactants that produce a majority [or another quantity?] of droplets that are less than 50 μm in diameter, or more preferably less than 10 μm in diameter, when the SEDDS compositions of the present invention form an emulsion. The polyethoxylated long chain or medium chain, saturated or unsaturated fatty acid triglycerides having HLB values greater than 10 are especially suitable for use in the present invention. Examples of such surfactants include polyoxyl 40 castor oil (Etocas 40), polyoxylethylene 40 hydrogenated castor oil (CREMOPHOR® RH40), polyoxylethylene 35 castor oil (CREMOPHOR® EL), and caprylocaproyl macrogol-8 glycerides (Labrasol). The Etocas 40 surfactant is available from Croda Chemicals, North Humberside, England. The CREMOPHOR® surfactants are available from the BASF Corporation, Mount Olive, NJ, USA. The Labrasol surfactant is available from Gattefosse Corporation, Westwood, NJ. These surfactants and others may be used in a formulation according to the present invention in any effective concentration, including, for example, in a concentration range of 5% to 80% (w/v).

Acceptable oil components include propylene glycol esters of medium chain fatty acids, such as propylene glycol dicaprylate/dicaprate, propylene glycol dipelargonate, and propylene glycol dilaurate. A preferred oil component is propylene glycol dicaprylate/dicaprate. The term "propylene glycol dicaprylate/dicaprate" is understood by those in the art to refer to a mixture containing propylene glycol dicaprylate, propylene glycol dicaprylate-caprate, and propylene glycol dicaprate, which may vary in the ratio of these components. An example of a commercially available form of propylene glycol dicaprylate/dicaprate is CAPTEX® 200, available from the Abitec Corp. (Columbus, OH, USA). The oil components may be used in the formulations of the present invention in any effective concentration, including, for example, in a concentration range of 5% to 80% (w/v).

Any effective non-aqueous protic solvent, or effective combinations thereof, may be used in accordance with the present invention. Acceptable non-aqueous protic solvents include any pharmaceutically acceptable mono-, di- or trihydroxy linear aliphatic and aromatic solvent, or effective combinations thereof. Examples of

non-aqueous protic solvents include ethanol, benzyl alcohol, propylene glycol, polyethylene glycols and glycerol. The protic solvents may be used in the formulations of the present invention in any effective concentration, including, for example, in a concentration range of 5% to 50% (w/v).

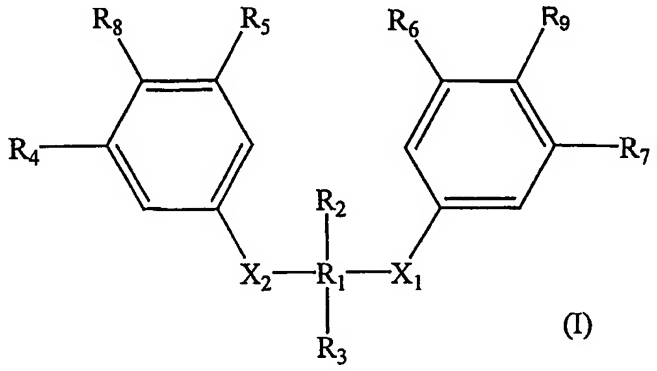
Suitable optional chelating agents include any pharmaceutically acceptable chelating agent, such as citric acid, maleic acid, succinic acid, tartaric acid, EGTA (ethylene glycol-bis(β-aminoethyl ether) tetraacetic acid, or egtazic acid) and EDTA (ethylene diamine tetraacetic acid, or edetic acid). Such chelating agents are commercially available in various forms, e.g., as sodium or potassium salts or as the free acids. Such chelating agents may be used in the formulations of the present invention in any effective concentration, including, for example, in a concentration range of between 0.01% and 10% (w/v). Effective chelating agents are those that generally enhance the stability of a hydrophobic drug in a SEDDS composition of the present invention, while not detrimentally affecting the SEDDS composition itself.

Any effective soluble antioxidant may optionally be used with the compositions of the present invention. Effective soluble antioxidants are pharmaceutically acceptable antioxidants that generally enhance the stability of a hydrophobic drug in a SEDDS composition of the present invention, while not detrimentally affecting the SEDDS composition itself. Suitable optional soluble antioxidants include α-tocopherol, tocopherol acetate, vitamin E polyethylene glycol succinate, propyl gallate, butylated hydroxytoluene and butylated hydroxanisole. These antioxidants generally differ from the phenolic antioxidants used as pharmaceutically active ingredients in the SEDDS of the invention in that they are generally more soluble in an aqueous solvent than the phenolic antioxidants. These antioxidants are also generally effective in removing or decreasing peroxide impurities. Soluble antioxidants may be used in the formulations of the present invention in any effective concentration, including, for example, in a concentration range of between 0.01% and 10% (w/v).

In another aspect, the present invention provides a pharmaceutical composition. The pharmaceutical compositions of the present invention include a SEDDS disclosed herein and one or more hydrophobic pharmaceutically active ingredients. Any effective pharmaceutically active ingredient may be used. Effective

pharmaceutically active ingredients include, for example, hydrophobic phenolic antioxidants having the general Formulae (I) and (II) as discussed below.

Compounds of Formula (I) have the structure:



(I)

wherein

X_1 and X_2 are independently selected from the group consisting of oxy and a dialkyl substituted silyl;

R_1 is alkyl; R_2 and R_3 are independently selected from the group consisting of H and an alkyl;

R_4, R_5, R_6, and R_7 are independently selected from the group consisting of H, methoxy, and a branched or straight chain alkyl; and

R_8 and R_9 are independently selected from the group consisting of hydrogen, hydroxy, trifluoromethyl, halide, amine, alkyl, alkenyl, aryl, heteroaryl, alkanoyl, aryloyl, heteroaryloyl,–O(alkyl), –OCO-(H or alkyl), –OCO-(alkenyl), –OCO-(aryl), –OCO-(heteroaryl), –(alkyl)-COOH, –(alkenyl)-COOH, –OCO-(alkyl)-COOH, –OCO-(alkenyl)-COOH, –CO-(alkyl)-COOH, and –CO-(alkenyl)-COOH;

wherein when the R_8 or R_9 substituents are alkyl, alkenyl, aryl, heteroaryl, alkanoyl, aryloyl, heteroaryloyl, –O(alkyl), –OCO-(H or alkyl), –OCO-(alkenyl), –OCO-(aryl), –OCO-(heteroaryl), –(alkyl)-COOH, –(alkenyl)-COOH, –OCO-(alkyl)-COOH, –OCO-(alkenyl)-COOH, –CO-(alkyl)-COOH, or –CO-(alkenyl)-COOH, they may be independently substituted with one or more functionalities independently selected from the group consisting of: C_1-C_6 alkyl, halogen, –OH, $–OCH_3$, $–OCH_2CH_3$, halomethyl, dihalomethyl, trihalomethyl, $–NH_2$, alkyl-substituted amino, $–NO_2$, –CN, –NC, –C(=NH)($-NH_2$) (*i.e.*, amidine), –SH, –COOH, $–COOCH_3$, and $–COOCH_2CH_3$.

In one embodiment, the methods comprise administering to a subject in need of treatment, a compound of Formula (I) wherein:

X_1 and X_2 are independently selected from the group consisting of oxy and a dialkyl substituted silyl;

R_1 is C_1-C_4 alkyl;

R_2 and R_3 are independently selected from the group consisting of H and a C_1-C_4 alkyl;

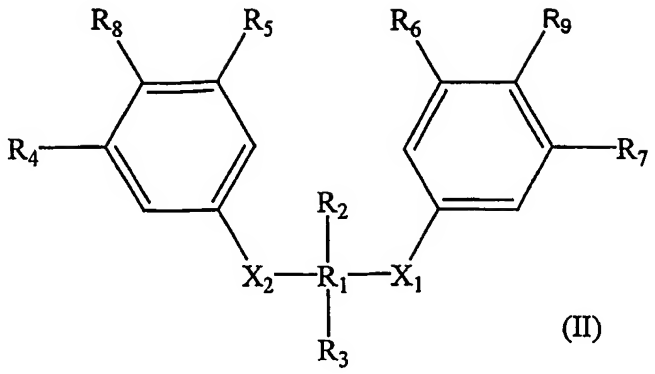
R_4, R_5, R_6, and R_7 are independently selected from the group consisting of H, methoxy, and a branched or straight chain C_1-C_6 alkyl; and

R_8 and R_9 are independently selected from the group consisting of hydrogen, hydroxy, trifluoromethyl, halide, amine, alkyl, alkenyl, aryl, heteroaryl, alkanoyl, aryloyl, heteroaryloyl, –O(C_1-C_6 alkyl), –OCO-(H or C_1-C_7 alkyl), –OCO-(C_3-C_7 alkenyl), –OCO-(aryl), –OCO-(heteroaryl), –(C_0-C_8 alkyl)-COOH, –(C_2-C_8 alkenyl)-COOH, –OCO-(C_0-C_6 alkyl)-COOH, –OCO-(C_2-C_6 alkenyl)-COOH, –CO-(C_0-C_6 alkyl)-COOH, and –CO-(C_2-C_6 alkenyl)-COOH;

wherein when the R_8 or R_9 substituents are alkyl, alkenyl, aryl, heteroaryl, alkanoyl, aryloyl, heteroaryloyl,–O(C_1-C_6 alkyl), –OCO-(H or C_1-C_7 alkyl), –OCO-(C_3-C_7 alkenyl), –OCO-(aryl), –OCO-(heteroaryl), –(C_0-C_8 alkyl)-COOH, –(C_2-C_8 alkenyl)-COOH, –OCO-(C_0-C_6 alkyl)-COOH, –OCO-(C_2-C_6 alkenyl)-COOH, –CO-(C_0-C_6 alkyl)-COOH, or –CO-(C_2-C_6 alkenyl)-COOH, they may be independently substituted with one or more functionalities independently selected from the group consisting of C_1-C_6 alkyl, halogen, –OH, $–OCH_3$, $–OCH_2CH_3$, halomethyl, dihalomethyl, trihalomethyl, $–NH_2$, alkyl-substituted amino, $–NO_2$, –CN, –NC, –C(=NH)($-NH_2$) (*i.e.*, amidine), –SH, –COOH, $–COOCH_3$, and $COOCH_2CH_3$.

Particular compounds of Formula (I) include those wherein R_4 and R_5 are tert-butyl, and R_8 is hydroxy. Further compounds of Formula (I) are those wherein X_1 and X_2 are independently selected from the group consisting of oxy and dimethyl-silyl; R_1 is methylene; R_2 and R_3 are hydrogen, R_4, R_5, R_6, and R_7 are independently selected from the group consisting of hydrogen and tert-butyl; and R_8 and R_9 are independently selected from the group consisting of hydroxy and methoxy.

In another embodiment, of the present invention the pharmaceutical compositions comprises a compound of Formula (II):



(II)

wherein

X_1 and X_2 are independently selected from the group consisting of thio, oxy, and a dialkyl substituted silyl;

R_1 is C_1-C_4 alkyl;

R_2 and R_3 are independently selected from the group consisting of H and a C_1-C_4 alkyl;

R_4, R_5, R_6, and R_7 are independently selected from the group consisting of H, methoxy, and a branched or straight chain alkyl; and

R_8 and R_9 are independently selected from the group consisting of hydrogen, hydroxy, trifluoromethyl, halide, amine, alkyl, alkenyl, aryl, heteroaryl, alkanoyl, aryloyl, heteroaryloyl,–O(alkyl), –OCO-(H or alkyl), –OCO-(alkenyl), –OCO-(aryl), –OCO-(heteroaryl), –(alkyl)-COOH, –(alkenyl)-COOH, –OCO-(alkyl)-COOH, –OCO-(alkenyl)-COOH, –CO-(alkyl)-COOH, and –CO-(alkenyl)-COOH;

wherein when the R_8 or R_9 substituents are alkyl, alkenyl, aryl, heteroaryl, alkanoyl, aryloyl, heteroaryloyl, –O(alkyl), –OCO-(H or alkyl), –OCO-(alkenyl), –OCO-(aryl), –OCO-(heteroaryl), –(alkyl)-COOH, –(alkenyl)-COOH, –OCO-(alkyl)-COOH, –OCO-(alkenyl)-COOH, –CO-(alkyl)-COOH, and –CO-(alkenyl)-COOH, they may be independently substituted with one or more functionalities independently selected from the group consisting of C_1-C_6 alkyl, halogen, –OH, $–OCH_3$, $–OCH_2CH_3$, halomethyl, dihalomethyl, trihalomethyl, $–NH_2$, alkyl-substituted amino. $–NO_2$, –CN, –NC, $–C(=NH)(-NH_2)$ (*i.e.*, amidine),

–SH, –COOH, $–COOCH_3$, and $–COOCH_2CH_3$.

In one embodiment, the methods comprise administering to a subject in need of treatment, a compound of Formula (II) wherein:

X_1 and X_2 are independently selected from the group consisting of thio, oxy, and a dialkyl substituted silyl;

R_1 is C_1-C_4 alkyl;

R_2 and R_3 are independently selected from the group consisting of H and a C_1-C_4 alkyl;

R_4, R_5, R_6, and R_7 are independently selected from the group consisting of H, methoxy, and a branched or straight chain C_1-C_6 alkyl; and

R_8 and R_9 are independently selected from the group consisting of hydrogen, hydroxy, trifluoromethyl, halide, amine, alkyl, alkenyl, aryl, heteroaryl, alkanoyl, aryloyl, heteroaryloyl, –O(C_1-C_6 alkyl), –OCO-(H or C_1-C_7 alkyl), –OCO-(C_3-C_7 alkenyl), –OCO-(aryl), –OCO-(heteroaryl), –(C_0-C_8 alkyl)-COOH, –(C_2-C_8 alkenyl)-COOH, –OCO-(C_0-C_6 alkyl)-COOH, –OCO-(C_2-C_6 alkenyl)-COOH, –CO-(C_0-C_6 alkyl)-COOH, and –CO-(C_2-C_6 alkenyl)-COOH;

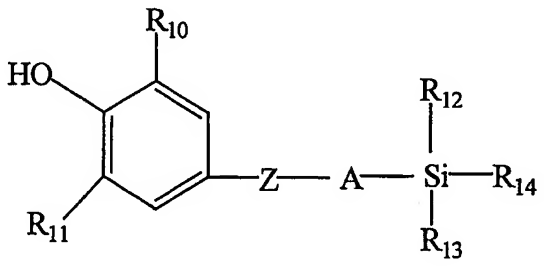
wherein when the R_8 or R_9 substituents are alkyl, alkenyl, aryl, heteroaryl, alkanoyl, aryloyl, heteroaryloyl, –O(C_1-C_6 alkyl), –OCO-(H or C_1-C_7 alkyl), –OCO-(C_3-C_7 alkenyl), –OCO-(aryl), –OCO-(heteroaryl), –(C_0-C_8 alkyl)-COOH, –(C_2-C_8 alkenyl)-COOH, –OCO-(C_0-C_6 alkyl)-COOH, –OCO-(C_2-C_6 alkenyl)-COOH, –CO-(C_0-C_6 alkyl)-COOH, and –CO-(C_2-C_6 alkenyl)-COOH, they may be independently substituted with one or more functionalities independently selected from the group consisting of C_1-C_6 alkyl, halogen, –OH, $–OCH_3$, $–OCH_2CH_3$, halomethyl, dihalomethyl, trihalomethyl, $–NH_2$, alkyl-substituted amino, $–NO_2$, –CN, –NC, –C(=NH)($-NH_2$) (*i.e.*, amidine), –SH, –COOH, $–COOCH_3$, and $–COOCH_2CH_3$.

Again, particular compounds are those wherein R_4 and R_5 are tert-butyl, and R_8 is hydroxy. More particularly, compounds of Formula (II) include those wherein X_1 and X_2 are thio; R_1 is methylene; R_2 and R_3 are methyl; R_4, R_5, R_6, and R_7 are tert-butyl; R_8 is hydroxy; and R_9 is butandioate (*i.e.*, succinic acid mono-{2,6-di-tert-butyl-4-[1-(3,5-di-tert-butyl-4-hydroxy-phenylsulfanyl)-1-methyl-ethylsulfanyl]-phenyl} ester).

Other embodiments include those wherein X_1 and X_2 are independently selected from the group consisting of thio and dimethyl-silyl; R_1 is methylene; R_2 and R_3 are independently selected from the group consisting of hydrogen and methyl; R_4, R_5, R_6, and R_7 are independently selected from the group consisting of hydrogen and

tert-butyl; and R_8 and R_9 are independently selected from the group consisting of hydrogen, hydroxy, methoxy, and butandioate; with the proviso that when X_1 and X_2 are both thio, R_8 and R_9 are not both hydroxy.

In another aspect, a pharmaceutical composition including a SEDDS of the present invention further includes one or more of a variety of phenolic antioxidants, included among such phenolic compounds are those disclosed in U.S. Patents No. 5,155,250; 5,962,435; and 5,677,291, the entireties of which are hereby incorporated by reference. Specifically, the phenolic antioxidants include those 2,6-di-alkyl-4-silyl-phenols having the general Formula (III)



(III)

wherein: R_{10}, R_{11}, R_{12} and R_{13} are each independently a C_1 - C_6 alkyl group;

Z is a thio, oxy or methylene group;

A is a C_1 - C_4 alkylene group; and

R_{14} is a C_1 - C_6 alkyl or $-(CH_2)_n-(Ar)$

wherein n is an integer 0, 1, 2 or 3; and Ar is phenyl or napthyl unsubstituted or substituted with one to three substituents selected from the group consisting of hydroxy, methoxy, ethoxy, chloro, fluoro or C_1 - C_6 alkyl group.

Compounds of Formula (III) can be prepared by methods known to those in the art, and particularly by the methods disclosed in U.S. Patent No. 5,155,250, particularly col. 3, line 12 through col. 8, line 44. Such compounds preferably have vascular protective properties, for example, or other therapeutic uses where antioxidant properties are desirable.

Specific examples of 2,6-di-alkyl-4-silyl-phenols include without limitation:

2,6-di-t-butyl-4[(triethylsilyl)methylthio]phenol

2,6-di-t-butyl-4[(diethylphenylsilyl)methylthio]phenol

2,6-di-t-butyl-4[{diethyl-(4-methoxyphenyl)silyl}methylthio]phenol

2,6-di-t-butyl-4[{diethyl-(2-methoxyphenyl)silyl}methylthio]phenol

2,6-di-t-butyl-4[(tripropylsilyl)methylthio]phenol

2,6-di-t-butyl-4[(dipropylphenylsilyl)methylthio]phenol

2,6-di-t-butyl-4[{dipropyl(4-ethoxyphenyl)silyl}methylthio]phenol

2,6-di-t-butyl-4[{dipropyl(2-ethoxyphenyl)silyl}methylthio]phenol

2,6-di-t-butyl-4[(triisopropylsilyl)methylthio]phenol

2,6-di-t-butyl-4[(diisopropylphenylsilyl)methylthio]phenol

2,6-di-t-butyl-4[{diisopropyl-(4-methoxyphenyl)silyl}methylthio]phenol

2,6-di-t-butyl-4[{diisopropyl-(2-methoxyphenyl)silyl}methylthio]phenol

2,6-di-t-butyl-4[(tributylsilyl)methylthio]phenol

2,6-di-t-butyl-4[(dibutylphenylsilyl)methylthio]phenol

2,6-di-t-butyl-4[{dibutyl-(4-ethoxyphenyl)silyl}methylthio]phenol

2,6-di-t-butyl-4[{dibutyl-(2-ethoxyphenyl)silyl}methylthio]phenol

2,6-di-t-butyl-4[(triisobutylsilyl)methylthio]phenol

2,6-di-t-butyl-4[(diisobutylphenylsilyl)methylthio]phenol

2,6-di-t-butyl-4[{diisobutyl-(4-methoxyphenyl)silyl}methylthio]phenol

2,6-di-t-butyl-4[{diisobutyl-(2-methoxyphenyl)silyl}methylthio]phenol

2,6-di-t-butyl-4[(tri-t-butylsilyl)methylthio]phenol

2,6-di-t-butyl-4[(di-t-butylphenylsilyl)methylthio]phenol

2,6-di-t-butyl-4[{di-t-butyl(4-ethoxyphenyl)silyl}methylthio]phenol

2,6-di-t-butyl-4[{di-t-butyl(2-ethoxyphenyl)silyl}methylthio]phenol

2,6-di-methyl-4[(trimethylsilyl)methylthio]phenol

2,6-di-methyl-4[(dimethylphenylsilyl)methylthio]phenol

2,6-di-methyl-4[{dimethyl-(4-methoxyphenylsilyl)}methylthio]phenol

2,6-di-methyl-4[{dimethyl-(2-methoxyphenylsilyl)}methylthio]phenol

2,6-di-methyl-4[(dibutylphenylsilyl)methylthio]phenol

2,6-di-methyl-4[{dibutyl-(4-ethoxyphenyl)silyl}methylthio]phenol

2,6-di-methyl-4[{dibutyl-(2-ethoxyphenyl)silyl}methylthio]phenol

2,6-di-methyl-4[(tri-t-butylsilyl)methylthio]phenol

2,6-di-methyl-4[(di-t-butylphenylsilyl)methylthio]phenol

2,6-di-methyl-4[{di-t-butyl-(4-methoxyphenyl)silyl}methylthio]phenol

2,6-di-methyl-4[{di-t-butyl-(2-methoxyphenyl)silyl}methylthio]phenol

2,6-di-ethyl-4[(trimethylsilyl)methylthio]phenol

2,6-di-ethyl-4[(dimethylphenylsilyl)methylthio]phenol

2,6-di-ethyl-4[(tri-t-butylsilyl)methylthio]phenol

2,6-di-ethyl-4[(di-t-butylphenylsilyl)methylthio]phenol

2,6-di-ethyl-4[{di-t-butyl-(4-methoxyphenyl)silyl}methylthio]phenol

2,6-di-ethyl-4[{di-t-butyl-(2-methoxyphenyl)silyl}methylthio]phenol

2,6-di-propyl-4[(trimethylsilyl)methylthio]phenol

2,6-di-propyl-4[(dimethylphenylsilyl)methylthio]phenol

2,6-di-propyl-4[(trimethylsilyl)methylthio]phenol

2,6-di-propyl-4[(dimethylphenylsilyl)methylthio]phenol

2,6-di-propyl-4[{dimethyl-(4-ethoxyphenyl)silyl}methylthio]phenol

2,6-di-propyl-4[{dimethyl-(2-ethoxyphenyl)silyl}methylthio]phenol

2,6-di-butyl-4[(trimethylsilyl)methylthio]phenol

2,6-di-butyl-4[(dimethylphenylsilyl)methylthio]phenol

2,6-di-methyl-4[(trimethylsilyl)methyloxy]phenol

2,6-di-methyl-4[(dimethylphenylsilyl)methyloxy]phenol

2,6-di-methyl-4[{dimethyl-(4-ethoxyphenyl)silyl}methyloxy]phenol

2,6-di-methyl-4[{dimethyl-(2-ethoxyphenyl)silyl}methyloxy]phenol

2,6-di-butyl-4[(triethylsilyl)methyloxy]phenol

2,6-di-butyl-4[(diethylphenylsilyl)methyloxy]phenol

2,6-di-butyl-4[{diethyl(4-methoxyphenyl)silyl}methyloxy]phenol

2,6-di-butyl-4[{diethyl(2-methoxyphenyl)silyl}methyloxy]phenol

2,6-di-t-butyl-4[(trimethylsilyl)methyloxy]phenol

2,6-di-t-butyl-4[(dimethylphenylsilyl)methyloxy]phenol

2,6-di-t-butyl-4[{dimethyl(4-methoxyphenyl)silyl}methyloxy]phenol

2,6-di-t-butyl-4[{dimethyl(2-methoxyphenyl)silyl}methyloxy]phenol

2,6-di-t-butyl-4[{dimethyl-(4-ethoxyphenyl)silyl)methyloxy]phenol

2,6-di-t-butyl-4[{dimethyl-(2-ethoxyphenyl)silyl)methyloxy]phenol

2,6-di-methyl-4[(trimethylsilyl)methyloxy]phenol

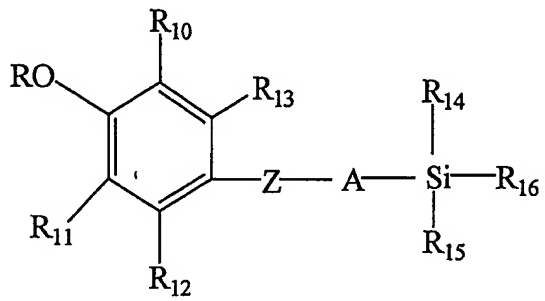
2,6-di-methyl-4[(dimethylphenylsilyl)methyloxy]phenol

2,6-di-butyl-4[(triethylsilyl)methyloxy]phenol

2,6-di-butyl-4[(diethylphenylsilyl)methyloxy]phenol

The above compounds are listed only to provide examples that may be used in the methods of the invention. Based upon the instant disclosure, the skilled artisan would recognize other compounds intended to be included within the scope of the presently claimed invention that would be useful in the methods recited herein.

In alternative embodiments of the invention it may be advantageous to employ compounds of Formula (I) or Formula (II) that are not also within the definition of compounds of Formula (IV), which is shown below.



(IV)

wherein:

R_{10} and R_{15} are each independently $C_1 - C_6$ alkyl;

R_{11}, R_{12} and R_{13} are each independently hydrogen or $C_1 - C_6$ alkyl;

R is hydrogen or $- C(O) - (CH_2)_m - Q$, wherein Q is hydrogen or –COOH and m is an integer 1, 2, 3 or 4;

Z is a thio, oxy or methylene group;

A is a $C_1 - C_4$ alkylene group;

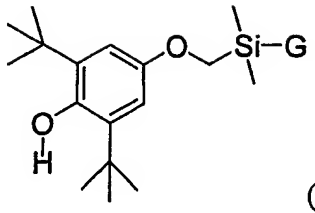
R_{14} and R_{16} are each independently a $C_1 - C_6$ alkyl or $- (CH_2)_n -(Ar)$, wherein n is an integer 0, 1, 2 or 3; and Ar is phenyl or naphthyl unsubstituted or substituted with one to three substituents selected from the group consisting of hydroxy, methoxy, ethoxy, halogen, trifluoromethyl, $C_1 - C_6$ alkyl, or $-NR_{17} R_{18}$, wherein R_{17} and R_{18} are each independently hydrogen or $C_1 - C_6$ alkyl; with the proviso that when R_{11} and at least one of R_{14} or R_{16} is $C_1 - C_6$ alkyl, and Ar is not substituted with trifluoromethyl or $-NR_{17} R_{18}$, then R is $- C(O) - (CH_2)_m - Q$; or a pharmaceutically acceptable salt thereof.

In another embodiment, it may be advantageous to employ compounds of Formula (I) or Formula (II) wherein at least one of R_8 or R_9 is independently selected from the group consisting of: trifluoromethyl, Br, amino, alkyl, alkenyl, aryl, heteroaryl, alkanoyl, aryloyl, heteroaryloyl, –O(C_1-C_6 alkyl), –OCO-(H or C_1-C_7 alkyl), –OCO-(C_3-C_7 alkenyl), –OCO-(aryl), –OCO-(heteroaryl), –(C_0-C_8 alkyl)-COOH, –(C_2-C_8 alkenyl)-COOH, –OCO-(C_0-C_6 alkyl)-COOH, –OCO-(C_2-C_6 alkenyl)-COOH, –CO-(C_0-C_6 alkyl)-COOH, and –CO-(C_2-C_6 alkenyl)-COOH; or any combination thereof. In other alternative embodiments useful in the methods of the invention, it may be advantageous to employ compounds of Formula (II) with the limiting proviso that when X_1 and X_2 are both thio, R_8 and R_9 are not both independently selected from hydroxy, ester, or ether; or alternatively, with the limiting proviso that when X_1 and X_2 are both thio, R_8 and R_9 are not both hydroxy.

It may additionally be advantageous to employ compounds of Formula (II) that are not a compound of Formula (IV) and which are subject to the proviso that when X_1 and X_2 are both thio, R_8 and R_9 are not both independently selected from hydroxy, ester, or ether; or alternatively, with the limiting proviso that when X_1 and X_2 are both thio, R_8 and R_9 are not both hydroxy.

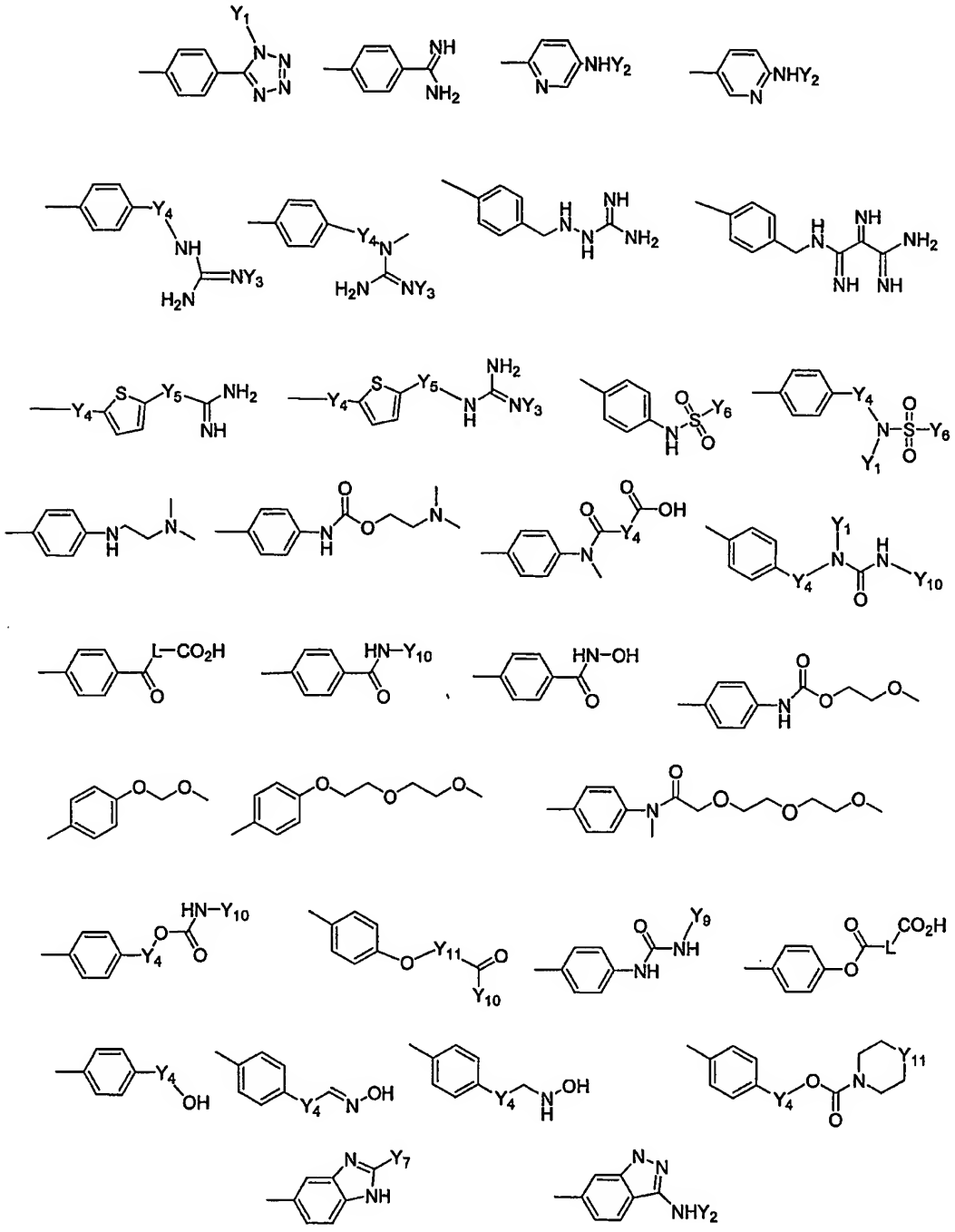
In another embodiment, it may be advantageous to employ compounds of Formula (II) subject to the limiting proviso that at least one of R_8 or R_9 is independently selected from the group consisting of: trifluoromethyl, Br, amino, alkyl, alkenyl, aryl, heteroaryl, alkanoyl, aryloyl, heteroaryloyl, –O(C_1-C_6 alkyl), –OCO-(H or C_1-C_7 alkyl), –OCO-(C_3-C_7 alkenyl), –OCO-(aryl), –OCO-(heteroaryl), –(C_0-C_8 alkyl)-COOH, –(C_2-C_8 alkenyl)-COOH, –OCO-(C_0-C_6 alkyl)-COOH, –OCO-(C_2-C_6 alkenyl)-COOH, –CO-(C_0-C_6 alkyl)-COOH, and –CO-(C_2-C_6 alkenyl)-COOH; or any combination thereof; and either the limiting proviso that when X_1 and X_2 are both thio, R_8 and R_9 are not both independently selected from hydroxy, ester, or ether, or alternatively, the limiting proviso that when X_1 and X_2 are both thio, R_8 and R_9 are not both hydroxy.

In a further embodiment, compounds of Formula (V), which is shown below, are provided. Compounds of Formula (V) are useful in the preparation of novel compositions and may be employed in conjunction with the SEDDS formulation of the present invention.



(V)

wherein G is selected from the group consisting of:



wherein:

Y_1 is –H, C_1-C_4 alkyl, or C_3-C_6 alkenyl;

Y_2 is –H, C_1-C_4 alkyl, or C_3-C_6 alkenyl, aryl, heteroaryl, aryloyl, alkanoyl, or heteroaryloyl;

Y_3 is –H, –CN, C_1-C_4 alkyl, C_3-C_6 alkenyl, aryl or heteroaryl;

Y_4 is $(CH_2)_n$, where n is 0-4, or C_3-C_6 alkenyl;

Y_5 is NH, $(CH_2)_n$, where n is 0-4, or C_2-C_6 alkenyl;

Y_6 is C_1-C_4 alkyl, C_3-C_6 alkenyl, aryl, heteroaryl, alkylaryl, or alkylheteroaryl;

Y_7 is H, C_1-C_4 alkyl, C_3-C_6 alkenyl, aryl, heteroaryl, alkylaryl, or alkylheteroaryl, or NH-Y_8;

Y_8 is C_1-C_4 alkyl, C_3-C_6 alkenyl, aryl, heteroaryl, alkylaryl, or alkylheteroaryl;

Y_9 is C_1-C_4 alkyl, C_3-C_6 alkenyl, aryl, or heteroaryl;

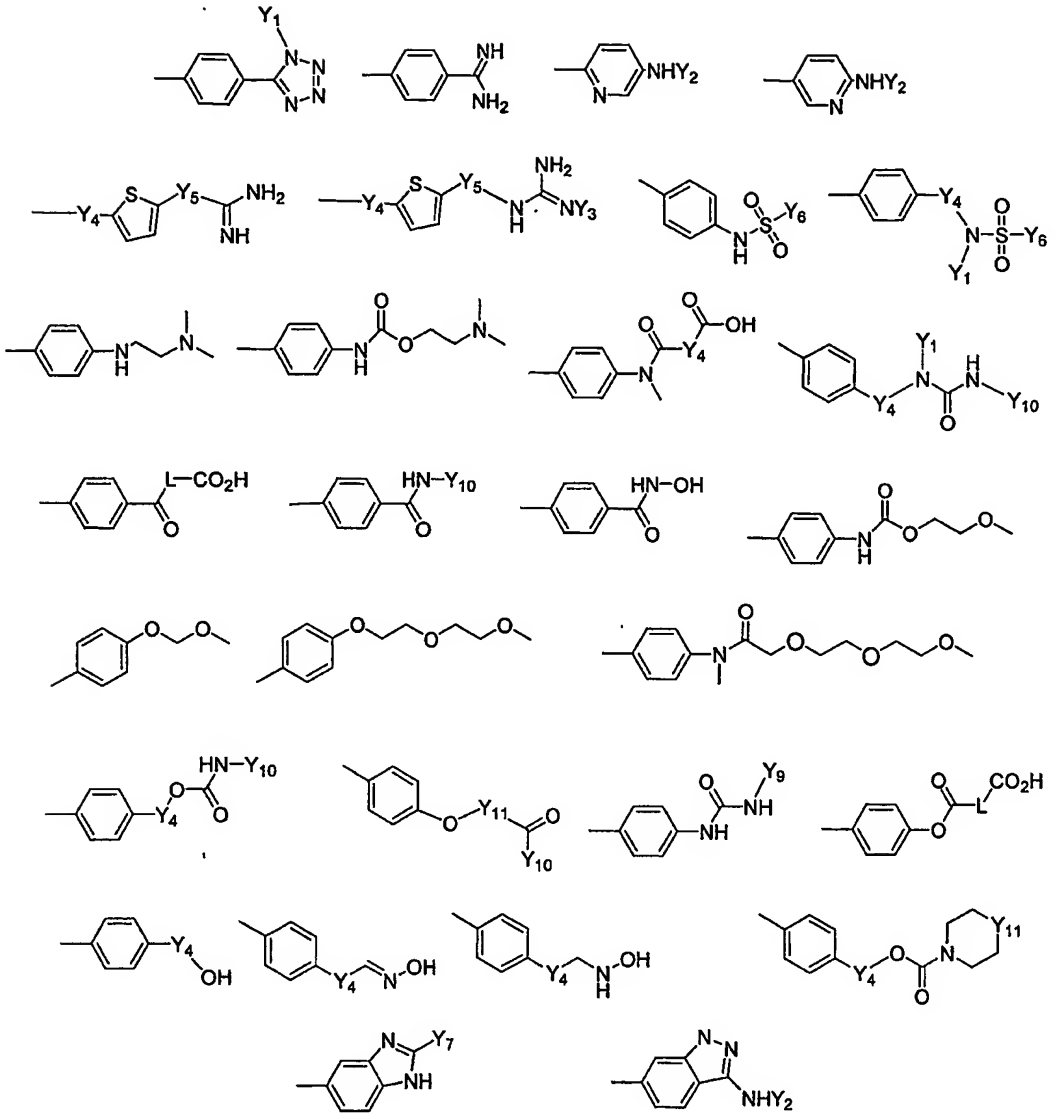
Y_{10} is H, C_1-C_4 alkyl, C_1-C_4 alkoxy, aryl, heteroaryl, alkylaryl, or alkylheteroaryl;

Y_{11} is C_1-C_4 alkyl, C_3-C_6 alkenyl, -O-, or -N-(Y_1);

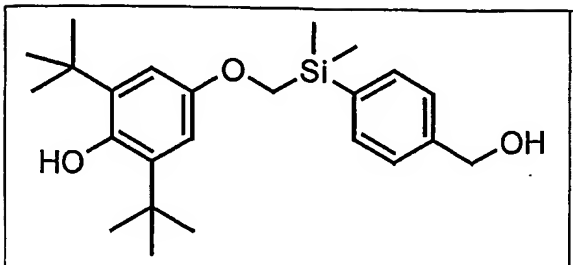
L is C_1-C_6 alkyl or C_2-C_6 alkenyl; and

wherein G may be additionally substituted with one or more substituents independently selected from the group consisting of –F, –Cl, –Br, –I, $–NH_2$, alkyl-substituted amino, –OH, –CN, –SH, $–CH_3$, $–CH_2CH_3$, $–CF_3$, $–OCH_3$, $–OCH_2CH_3$, –COOH, $–COOCH_3$, and $–COOCH_2CH_3$.

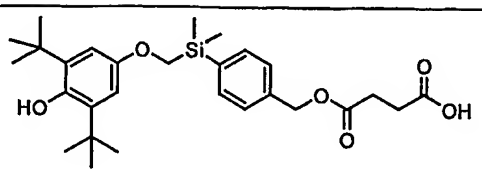
In one embodiment of Formula (V), G does not include any guanidine groups. Alternatively, in an embodiment of Formula (V), G is selected from:



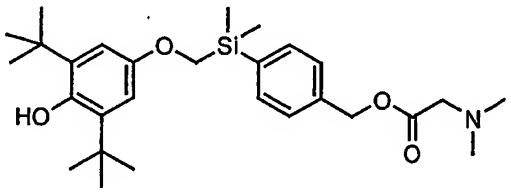
Certain compounds of the invention include:



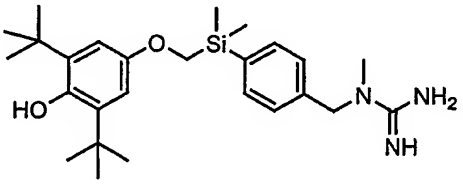
C1



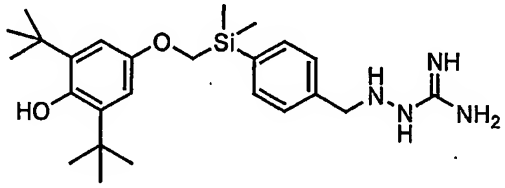
C2



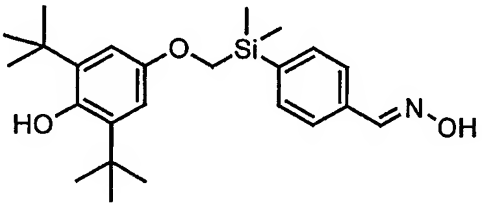
C3



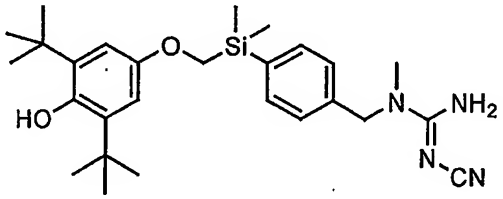
C4



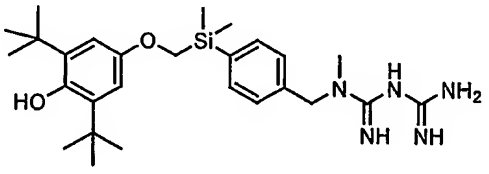
C5



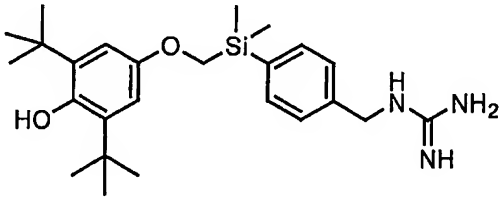
C6



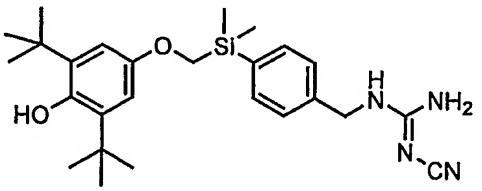
C7



C8



C9



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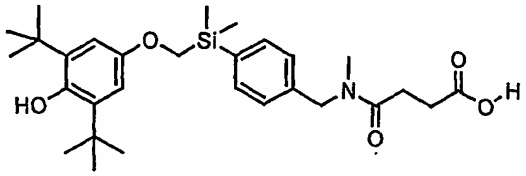

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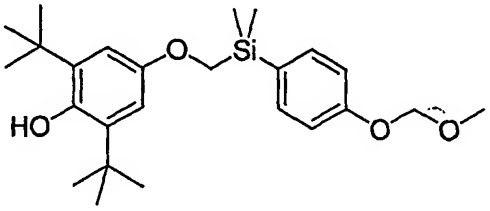

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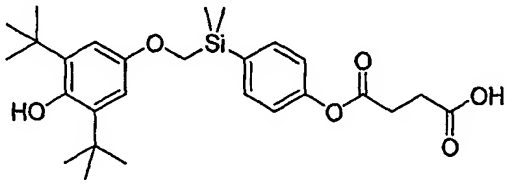

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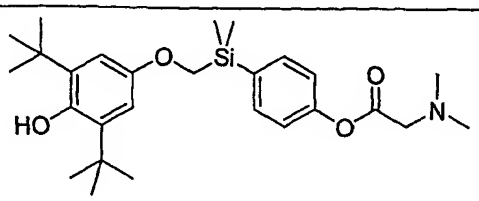
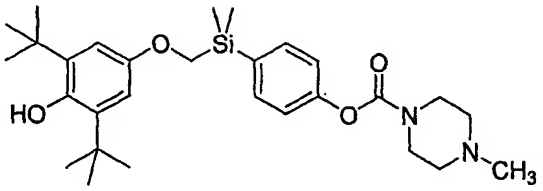
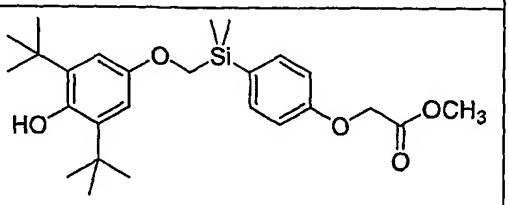


C14



C15



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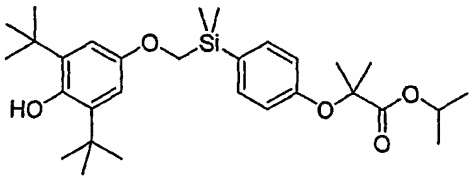
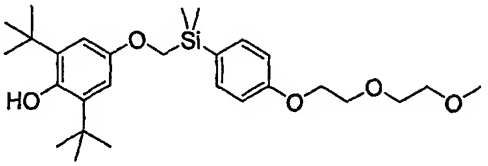


C17



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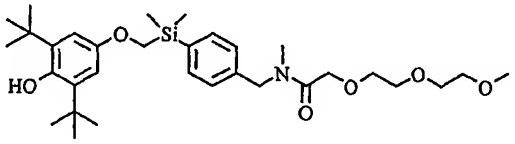

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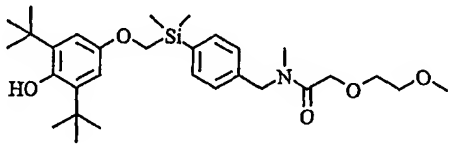

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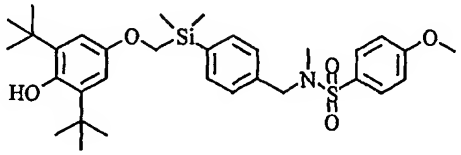

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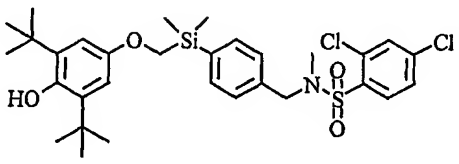

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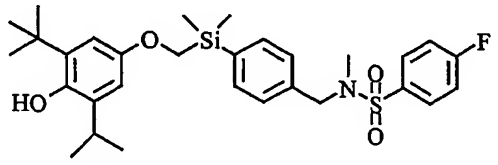

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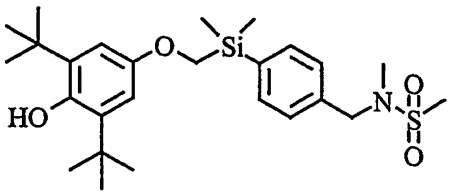

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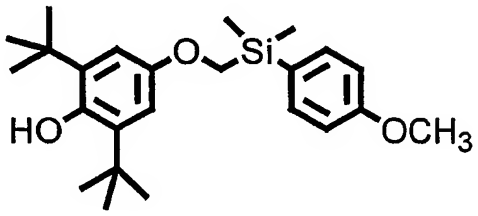


C25

Such compounds, as well as the compounds of Formulas (I)-(V) are described in International Application No.. [awaiting serial number], entitled "Methods and Compositions for Promoting Vascular Health", attorney docket no. 18528.738, filled concurently herewith, the disclosure of which is hereby incorporated by reference in its entirety.

For the purposes of this invention, where one or more functionalities encompassing R_1-R_{14}, Y_1-Y_{10}, L, Z, A, and Ar, are incorporated into a molecule of Formulas (I) - (V), each the functionality appearing at any location within the structures of Formulas (I) - (V) may be independently selected, and as appropriate, independently substituted.

Where a more generic substituent is set forth for any position in the molecules of the present invention, it is understood that the generic substituent may be replaced with more specific substituents, and the resulting molecules are within the scope of the molecules of the present invention. Thus, for example if a substituent is recited as an alkyl group, molecules, and groups of molecules, having the substituent limited to C_1-C_6 alkyl are understood to be part of the present invention. Similarly, if more than one substituent is recited generically, then each may be replaced by more specifically recited substituents, and the resulting molecules are within the scope of the molecules of the present invention. Thus, for example, if the molecule recites a first substituent as alkenyl and second substituent as alkylaryl, it is understood that the first substituent

may for example be limited to -($C_5 - C_{10}$ alkenyl) and the second may be limited to -(C_1-C_6 alkyl)-naphthalene.

As used herein, the term "alkyl" generally refers to saturated hydrocarbyl radicals of straight, branched or cyclic configuration including methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, n-hexyl, cyclohexyl, n-heptyl, octyl, n-octyl, and the like. Di-substituted alkyl generally refers to a hydrocarbyl radical substituted on its core with at least two substituents, R_2 and R_3. In some embodiments, alkyl substituents may be include $C_1 - C_{20}$ alkyl, $C_1 - C_{10}$ alkyl, $C_1 - C_8$ alkyl, C_1 - C_6 alkyl, or $C_5 - C_{10}$ alkyl.

As used herein, the terms halomethyl, dihalomethyl, or trihalomethyl refer to methyl radicals bearing one, two or three halogen substitutions, respectively.

The term "C_1 - C_4 alkylene" refers to a saturated hydrocarbyldiyl radical of straight or branched configuration made up of from one to four carbon atoms. Included within the scope of this term are methylene, 1,2-ethane-diyl, 1,1-ethane-diyl, 1,3-propane-diyl, 1,2-propanediyl, 1,3-butane-diyl, 1,4-butane-diyl and the like.

As used herein, the term alkenyl generally refers to hydrocarbyl radicals of straight, branched or cyclic configuration having at least one carbon-carbon double bond in either the *cis* or *trans* configuration, or as a mixture of *cis* and *trans* isomers (*i.e.*, the radical of an alkene). Included in the scope of alkenyl are substituents having from three to about eight carbon atoms ($C_3 - C_8$ alkenyl), from four to six carbon atoms ($C_4 - C_6$ alkenyl), or from five to about ten carbons ($C_5 - C_{10}$ alkenyl). Examples of alkenyl substituents include -$CHCH_2$ group (*i.e.*, ethylene), a propen-1-yl group, a propen-2-yl group, and a *trans* -$CH_2CHCHCH_3$ group (*i.e.*, *trans*-2-butene).

As used herein, aryl refers to a carbocyclic aromatic ring structure. Included in the scope of aryl groups are aromatic rings having from six to twenty carbon atoms. In some embodiments, they may have from ten to twenty carbon atoms, and in others from fourteen to 24 carbon atoms. Examples of aryl groups that may be incorporated as substituents include phenyl, phenanthryl (*i.e.*, phenanthrene), and napthyl (*i.e.*, napthalene) ring structures.

As used herein, heteroaryl refers to cyclic aromatic ring structures in which one or more atoms in the ring, the heteroatom(s), is an element other than carbon. Heteroatoms are typically O, S or N atoms. Included within the scope of heteroaryl,

and independently selectable are O, N, S and P heteroaryl ring structures. In some embodiments, the heteroaryl groups may be selected from heteroaryl groups that contain two or more heteroatoms, three or more heteroatoms, or four or more heteroatoms. Heteroaryl ring structures may be selected from those that contain five or more atoms, six or more atoms, or eight or more atoms. Examples of heteroaromatic ring structures that may be incorporated as substituent groups include, but are not limited to: acridine, benzimidazole, benzoxazole, benzofuran, 1,3-diazine, 1,2-diazine, 1,2-diazole, 1,4-diazanaphthalene, furan, furazan, imidazole, indole, isoxazole, isoquinoline, isothiazole, oxazole, purine, pyridazine, pyrazole, pyridine, pyrazine, pyrimidine, pyrrole, quinoline, quinoxaline, thiazole, thiophene, 1,3,5-triazine, 1,2,4-triazine, 1,2,3-triazine, tetrazole and quinazoline.

As used herein, the structure –O(alkyl) represents an alkylether, where alkyl is defined as above. Included in the scope of alkylether substituents are –O(C_1-C_6 alkyl), –O(C_2-C_8 alkyl), and –O(C_4-C_{10} alkyl). Examples of alkyl ethers include methoxy (*i.e.*, -OCH_3,), ethoxy (*i.e.*, -OCH_2CH_3,), and tert-butyl ethers (*i.e.*, -$OC(CH_3)_3$).

As used herein, the structure –OCO-(H or alkyl) represents an alkyl ester group, where alkyl is defined as above. When the structure is –OCO-(H), the substituent group will be a formate ester. Included in the scope of alkylesters are -OCO-(H or C_1-C_7 alkyl), –OCO-(H or C_3-C_9 alkyl), -OCO-(C_1-C_7 alkyl), and –OCO-(C_3-C_9 alkyl). Examples of alkyl esters include –$OCOCH_3$ (*i.e.*, acetoxy), –$OCOCH_2CH_3$ (*i.e.*, propionate ester).

As used herein, the structure –OCO-(alkenyl) represents an alkenyl ester group, where alkenyl is defined as above. Included in the scope of alkenyl esters are -OCO-(C_2-C_8 alkenyl), -OCO-(C_3-C_8 alkenyl), and –OCO-(C_5-C_9 alkenyl). Alkenyl esters maybe in the *cis* or *trans* isomers or mixtures of both *cis* and *trans* isomers. Examples of alkenyl esters include –$OCOCHCHCH_3$ (*i.e.*, 2-butenoate), –$OCOCHCHCH_2CH_3$ (*i.e.*, 2-pentenoate).

As used herein, the structure –(alkyl)-COOH generally refers to saturated hydrocarboxyl radicals (alkyl carboxylic acid) of straight, branched, or cyclic configuration, with –(C_0-C_8 alkyl)-COOH radicals having between one and nine carbon atoms in total. Included in the scope of alkylesters are –(alkyl)-COOH

radicals having between one and nine carbon atoms –(C_0-C_8 alkyl)-COOH, or between five and twelve carbon atoms –(C_4-C_{11} alkyl)-COOH. Such hydrocarboxyl radicals include methanoic acid, ethanoic acid, propanoic acid, butanoic acid, 2-methyl propanoic acid, pentanoic acid, 3-methyl butanoic acid, 2,2-dimethyl propanoic acid, and the like. Likewise, the structure –(alkenyl)-COOH generally refers to saturated hydrocarboxyl radicals where alkenyl is defined above. In addition to those alkyl esters recited as included in the scope of –(alkyl)-COOH above, in some embodiments, the group may be selected from structures with three to nine carbon atoms –(C_2-C_8 alkenyl)-COOH, and in other embodiments, the group may be selected from structures having five to ten carbon atoms –(C_4-C_9 alkenyl)-COOH.

As used herein, the structure –OCO-(alkyl)-COOH (alkyl dicarboxylic acid) generally refers to saturated hydro-dicarboxyl radicals of straight, branched or cyclic configuration, and –OCO-(C_0-C_6 alkyl)-COOH generally refers to dicarboxylic acids having between two and eight carbon atoms. Alkyl dicarboxylic acids may be selected from structures within the scope of –OCO-(alkyl)-COOH, including the structures -OCO-(C_0-C_6 alkyl)-COOH, –OCO-(C_0-C_8 alkyl)-COOH, and –OCO-(C_5-C_{10} alkyl)-COOH. Alkyl dicarboxylic acids include ethandioic acid, propandioic acid, butandioic acid (*e.g.*, succinic acid, 2-methyl-propandioic acid, pentandioic acid (*i.e.*, glutaric acid), 3-methyl-butandioic acid, hexandioic acid, and the like).

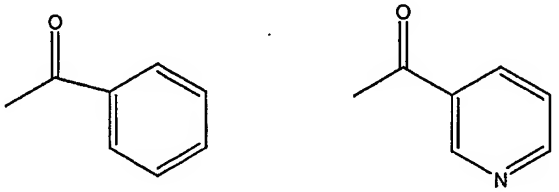
As used herein, the structure –OCO-(alkenyl)-COOH generally refers to hydro-dicarboxyl radicals having at least one carbon-carbon double bond of straight, branched or cyclic configuration. Carbon-carbon double bonds may be in the *cis* or *trans* configuration or may be present as a mixture of *cis* and *trans* isomers. Alkenyl oxydicarbonyls (alkenyl dicarboxylic acids) may selected from structures included within the scope of –OCO-(alkenyl)-COOH including the structure –OCO-(C_2-C_6 alkenyl)-COOH, where the group has up to eight carbon atoms and the structure –OCO-(C_5-C_{10} alkenyl)-COOH where it has up to twelve carbon atoms. Alkenyl oxydicarbonyls include *trans*-2-butenedioic acid (*e.g.*, fumaric acid, *cis*-2-butenedioic acid (*i.e.*, maleic acid), 2-pentenedioic acid, 3-methyl-2-pentenedioic 2-pentendioic butandioic acid, hexandioic acid, and the like).

As used herein, –CO–(alkyl)–COOH and –CO–(alkenyl)-COOH represent saturated and unsaturated ketocarboxylic acid radicals of straight, branched or cyclic

configuration where alkyl and alkenyl are as defined above. Ketocarboxylic acids may be independently selected from structures included within the scope of structures –CO–(alkyl)–COOH and –CO–(alkenyl)-COOH. Alkyl ketocarboxylic acids can be selected from –CO–(C_0-C_6 alkyl)–COOH and –CO–(C_3-C_9 alkyl)–COOH. Alkenyl ketocarboxylic acids can be selected from –CO–(C_2-C_6 alkenyl)-COOH and –CO–(C_4-C_{10} alkenyl)-COOH. Ketoalkyl carboxylic acids of the form –CO–(alkyl)–COOH include 6-keto-hexanoic acid, 5-keto-pentanoic, 5-keto-3-metyl-pentanoic, 3-keto-propanoic acid, and 2-keto-ethanoic acid. Ketoalkenyl carboxylic acids of the form –CO–(alkenyl)-COOH include 4-keto-2-butenoic acid, 5-keto-3-pentenoic acid, 6-keto-3-hexenoic acid, and 6-keto-3-methyl-2,4-hexadienoic acid.

As used herein, alkanoyl generally refers to a group with the structure –CO-(H or alkyl), where alkyl is defined above. When the group is of the form –COH the group will be an aldehyde. Alkanoyl groups included within the structure of –CO-(H or alkyl) include those with one to twenty carbons –CO-(C_1-C_{20} alkyl). In other embodiments, alkanoyl groups may be selected from those with three to twenty carbon atoms, CO-(C_3-C_{20} alkyl), or from five to twenty carbon atoms, CO-(C_5-C_{20} alkyl), or from seven to twenty carbon atoms CO-(C_7-C_{20} alkyl).

As used herein, aryloyl refers to a structure of the form –CO-(aryl), where aryl is defined as above. Similarly, heteroaryloyl refers to a group of the formula –CO-(heteroaryl), where heteroaryl is defined as above. Aryloyl and heteroaroyl groups may be independently selected to contain the aryl and heteroaryl groups recited above. Examples of aryloyl and heteroaryloyl groups include the following structures:



As used herein, the structures –OCO-(aryl) and –OCO-(heteroaryl) generally refer to aromatic and heteroaromatic carboxylic acid functionalities (aryloxy and heteroaryloxy) addition that are present as ester substituents, where aryl and heteroaryl are as described above. The –OCO-(aryl) and –OCO-(heteroaryl) groups may be independently selected to contain the aryl and heteroaryl groups recited

above. Aryl carboxylic acids include –OCO-phenyl, (*i.e.*, benzoate esters), and the like. Heteroaromatic carboxylic acid functionalities include 2-carboxy-pyridine, 2-carboxy-pyrrole, and 2-carboxy-furan.

For the purposes of this invention, halo substituents may be independently selected from the halogens such as fluorine, chlorine, bromine, iodine, and astatine.

Also included within the scope of the present invention are pharmaceutically acceptable salts, hydrates, solvates, clathrates, racemates, stereoisomers, or polymorphs of the compounds of the invention.

In animal studies, 2,6-di-alkyl-4-silyl-phenols have been shown to reduce serum low density lipids (LDLs), but not serum high density lipids (HDLs), to inhibit lipoprotein oxidation, and to inhibit cell adhesion molecules in vascular cells. Preclinical data indicate multiple modes of action on a cascade of events generally thought to be involved in the initiation and growth of atherosclerotic lesions. In animal models of atherosclerosis, 2,6-di-alkyl-4-silyl-phenols were orally active, lowered serum cholesterol concentrations, inhibited the formation of atherosclerotic plaques in the arterial wall, and prevented cholesterol-induced damage to vascular function. These effects appear to involve the ability of the compounds to lower serum cholesterol as well as other effects independent of cholesterol lowering.

In another aspect, a method for treating a disease or condition includes the steps of administering to a patient in need of such treatment, a pharmaceutical composition comprising a SEDDS of the present invention, in which is dissolved one or more effective phenolic antioxidants. In another aspect, the pharmaceutical composition may be administered as a prophylactic measure, rather than a therapeutic measure. The pharmaceutical compositions may be used for any effective purpose, including, for example, in the treatment or prevention of atherosclerosis (e.g., according to U.S. Patent No. 5,155,250), to lower plasma cholesterol levels in a patient at risk for or suffering from hypercholesterolemia (e.g., according to U.S. Patent No. 5,962,435), and to treat or prevent vascular occlusive disorders.

Any effective criteria may be used to determine that a patient may benefit from administration of a pharmaceutically active composition comprising a SEDDS of the present invention. Methods for the diagnosis of vascular occlusive disorders, including atherosclerosis and hypercholesterolemia, as well as procedures for the

identification of individuals at risk for development of these diseases or disorders, are well known to those in the art. Such procedures may include clinical tests, physical examination, personal interviews and assessment of family history. Treatment or prevention of these diseases involves administration of a therapeutically or prophylactically effective amount of the pharmaceutical composition of the invention. A "therapeutically effective amount" is considered to be that amount which effects a reduction in one or more symptoms or effects associated with the disease condition. A "prophylactically effective amount" is considered to be that amount that improves or prevents a change or worsening in a parameter useful in the prediction of the development of the disease condition. The determination of therapeutically or prophylactically effective amounts of the pharmaceutical composition of the invention is accomplished through conventional techniques. Factors to be considered in determining the appropriate dose for each patient include, but are not limited to the patient's age, weight, and gender; the gravity of the patient's condition; the route of administration; the elements of the pharmaceutical composition, particularly the identity of the therapeutic phenolic antioxidant; and the effect of or on any other medications being taken by the patient. Generally, an amount of the pharmaceutical composition that results in administration of between 0.1 milligram per kg body weight per day and 5 g per kg body weight per day of the phenolic antioxidant should be considered in treatment or prophylaxis. Preferably, the amounts considered will be in the range of about 1 mg/kg/day to 500 mg/kg/day.

The compositions of the present invention may be administered in any mode and form which makes a pharmaceutically active compound biologically available to the patient in effective amounts. The compositions may be administered via oral, parenteral, transdermal, transmucosal or intranasal routes, as well as others known to those in the art. Particularly useful is oral administration. Determination of the appropriate administration method is usually made upon consideration of the disease to be treated, the stage of the disease, the comfort of the patient, and other factors.

When orally administered, the pharmaceutical compositions may be in any effective form, including, for example, of suspensions, syrups, troches, elixirs, wafers, chewing gums, compressed tablets, or soft or hard starch or gelatin capsules. Often, they are in bulk liquid or in the form of liquid oral unit dosage forms, such as filled

pouches or gelatin capsules. Upon dissolution of the capsules, the pharmaceutical composition forms an emulsion that is absorbed, e.g., via the lymphatic system, and carried away through the thoracic duct, bypassing the liver. The capsules may be enteric-coated using materials and methods known to those in the art. For example, commercially available enteric polymer coatings are available from Eastman Chemical Products, Kingsport, TN, USA, under the trade names C-A-P™ (cellulose acetate phthalate) and C-A-T (cellulose acetate trimellitate).

The compressed tablet formulations may also contain one or more of the following agents: binders, such as gelatin, corn starch, polyvinylpyrrolidone or gum tragacanth; fillers, such as microcrystalline cellulose or lactose; disintegrating agents, such as croscarmellose sodium and sodium starch glycolate, sweeteners, such as saccharine or sucrose; and various flavoring agents. When in the form of a capsule, the formulation may also contain a liquid carrier, such as a fatty oil or polyethylene glycol. Other dosage forms may also incorporate other materials to modify the form of the unit, for example, coatings. The materials used should be of a grade and quality suitable for use in pharmaceutical preparations.

If administered other than orally, the pharmaceutical compositions may be injected, e.g., subcutaneously, intraperitoneally, intramuscularly, or intravenously. Exemplary surfactants for parenteral administration are polyethoxylated glycerides containing a fatty acid moiety other than ricinoleic acid or hydrogenated ricinoleic acid in order to avoid potential anaphylactic reactions. An example of a polyethoxylated glycerides is caprylocaproyl macrogol-8 glycerides (Labrasol). The pharmaceutical compositions may be administered in the form of a solution or as an emulsion. The solutions or emulsions may contain one or more of the following carriers or additions: sterile diluents for injection, such as, water or saline; polyethylene glycols; glycerine; propylene glycol or other protic solvents; antibacterial, antifungal or antimicrobial agents, such as, benzyl alcohol; buffers, such as acetates, citrates or phosphates; and tonicity adjustment agents, such as, sodium chloride or dextrose. As noted above, pharmaceutically acceptable forms of each agent should be used. In addition, sterile forms of each component may be added together under aseptic conditions, but it is preferred, where possible, to sterilize the pharmaceutical composition after it is prepared (terminal sterilization).

In another aspect, the pharmaceutical composition of the invention is prepared by adding a phenolic antioxidant to a SEDDS that includes propylene glycol dicaprylate/dicaprate, polyoxyl 40 hydrogenated castor oil, and dehydrated alcohol. Into this SEDDS vehicle is added citric acid (anhydrous) and butylated hydroxytoluene. In a particularly preferred embodiment, the phenolic antioxidant is a 2,6-di-alkyl-4-silyl-phenol. The concentration ranges of the components of this pharmaceutical composition and the exemplary compositions are listed in Table 1.

Table 1. 2,6-Di-Alkyl-4-Silyl-Phenol in SEDDS Composition

Ingredient	Composition (% w/v)	Preferred Composition (% w/v)
2,6-di-alkyl-4-silyl-phenol	1.0 – 10.0	5.00
Butylated Hydroxytoluene, NF	0.01 – 10.0	0.04
Citric Acid (Anhydrous), USP	0.01 – 10.0	0.10
Dehydrated Alcohol, USP	5.0 – 50.0	12.44
Polyoxyl 40 Hydrogenated Castor Oil, NF	10.0 – 80.0	26.66
Propylene Glycol Dicaprylate/Dicaprate	5.0 – 80.0	49.76
Total	100.0	100.0

The volume mean droplet size of the emulsion prepared by mixing the SEDDS composition with 0.1N hydrochloric acid is typically approximately 1 μm, with at least about 95% of the droplets usually in the range from 0.16 μm to 35 μm. The mean droplet size may vary when the SEDDS formulation is mixed with an aqueous beverage before oral consumption, but will often be on the order of 1-5 μm.

In some instances it may be required to reduce or prevent oxidation of the 2,6-di-alkyl-4-silyl-phenol or other therapeutic compound. Suitable procedures to reduce or prevent oxidation include the addition of a chelating agent, such as citric acid, to chelate heavy metal impurities that can catalyze the oxidation reaction. In addition or in the alternative, another antioxidant, such as butylated hydroxytoluene, may be added to eliminate the effect of peroxide impurities. The compositions may also be sparged with nitrogen, argon, or another inert gas, and a vessel in which the composition is stored may be sealed with a nitrogen or argon headspace to eliminate

or minimize the oxygen content of the solution. Finally, the compositions may be stored in dark containers to provide protection from light.

The SEDDS vehicle of the current invention may be prepared in any effective manner. In one embodiment, the SEDDS of the invention may be prepared by mixing the hydrophilic surfactant and the digestible oil component, followed by adding the non-aqueous protic solvent to form a clear isotropic mixture. The optional chelating agent is added as a solution in the protic solvent, and the optional antioxidant is then added to the solution mixture. For the preparation of drug-containing SEDDS solution, the drug can be added to the SEDDS vehicle solution. For example, the compositions presented in Table 1 can be prepared as follows: Polyoxyl 40 hydrogenated castor oil is first mixed with most (90% or more) of the propylene glycol dicaprylate/dicaprate. To this mixture, a solution of the citric acid anhydrous in the dehydrated alcohol is added and the mixture is mixed to form a clear solution. Then, the butylated hydroxytoluene and the 2,6-di-alkyl-4-silyl-phenol are consecutively added and mixed until each is completely dissolved in the solution. The remaining propylene glycol dicaprylate/dicaprate is added to the final batch quantity. The solution may be filtered through a suitable filter membrane to ensure clarity of the solution.

Example 1:

The stability of a 2,6-di-alkyl-4-silyl-phenol in a preferred SEDDS composition (Table 1), without the antioxidant (i.e., without butylated hydroxytoluene), was studied by storing the SEDDS composition in amber glass ampoules with a nitrogen or air headspace for periods between 15 and 97 days, at 25 °C and 40 °C. The stability of the phenolic antioxidant was determined by an HPLC assay, and is expressed as the percent of initial potency measured. The results are shown in Table 2.

Table 2. 2,6-Di-Alkyl-4-Silyl-Phenol Stability in Preferred SEDDS Composition without Antioxidant

Temperature	Headspace	Initial Potency	Potency (% initial potency)				
			15 Days	30 Days	45 Days	60 Days	97 Days
25 °C	Air	100.0	101.2	95.9	97.0	97.7	95.2
	Nitrogen	100.0	101.8	96.7	97.6	101.6	101.2
40 °C	Air	100.0	98.3	93.6	90.8	88.8	86.8
	Nitrogen	100.0	101.1	98.8	101.4	96.9	98.8

Table 2 shows that a 2,6-di-alkyl-4-silyl-phenol, in the SEDDS composition of the present invention, without the antioxidant butylated hydroxytoluene, degraded in the presence of air, but was relatively stable when stored under a nitrogen headspace. The rate and extent of degradation were greater at the elevated temperature of 40 °C.

Example 2:

In another stability study, a batch of 2,6-di-alkyl-4-silyl-phenol in a preferred SEDDS composition with the antioxidant butylated hydroxytoluene was prepared with nitrogen sparging and stored under a nitrogen headspace. A second batch was prepared without nitrogen sparging and stored under air. Samples were stored at 5 °C, 25 °C, and 40 °C, for periods up to 53 weeks. The stability of the phenolic antioxidant in the two storage conditions was measured as described in Example 1, with replicate measurements of each sample. The results are shown in Table 3.

Table 3. 2,6-Di-Alkyl-4-Silyl-Phenol Stability in Preferred SEDDS Composition at 5°C, 25°C and 40°C

Temp	Head-space	Potency (% of Label Claim)							
		Initial	2 Wk	4 Wk	8 Wk	13 Wk	26 Wk	39 Wk	53 Wk
	Air	101.1 101.3	-	-	-	-	-	-	-
	Nitrogen	100.3 100.9	-	-	-	-	-	-	-
5 °C	Air	-	101.2 99.9	100.9 100.8	100.9 100.6	101.0 101.5	101.9 100.9	101.2 101.3	100.9 100.8
	Nitrogen	-	100.8 99.8	101.5 101.4	99.8 100.1	100.5 101.1	101.2 101.0	100.8 101.0	100.3 100.1
25 °C	Air	-	101.7 102.0	101.0 100.9	100.1 100.5	100.5 100.4	99.4 99.4	100.0 100.5	99.0 97.8
	Nitrogen	-	100.5 100.6	99.0 100.5	99.9 100.2	100.6 100.0	100.0 100.1	99.1 98.5	99.9 97.2
40 °C	Air	-	101.0 101.0	100.4 100.5	99.8 100.1	100.2 100.1	-	-	-
	Nitrogen	-	100.4 100.4	101.9 100.6	99.3 99.9	100.4 100.3	-	-	-

Table 3 shows that, in the presence of the soluble antioxidant butylated hydroxytoluene, the 2,6-di-alkyl-4-silyl-phenol was stable in the SEDDS under either a nitrogen or air headspace. The compound was stable up to 13 weeks at elevated temperature (40 °C) and 53 weeks at 5 °C and 25 °C conditions. Thus, the SEDDS formulation of the present invention provides a stable environment for phenolic antioxidants such as a 2,6-di-alkyl-4-silyl-phenol, particularly in the presence of a suitable antioxidant.

Example 3:

The bioavailability of a 2,6-di-alkyl-4-silyl-phenol in a SEDDS composition of the invention was compared to its bioavailability in a variety of other formulations. A 2,6-di-alkyl-4-silyl-phenol was formulated in a SEDDS of the present invention containing 52.6% (w/v) propylene glycol dicaprylate/dicaprate as the oil component, 28.2 %w/w polyoxyl 40 hydrogenated castor oil as the surfactant, and 13.1 % (w/v) dehydrated alcohol (SEDDS A). For comparison, the 2,6-di-alkyl-4-silyl-phenol was formulated in a) a SEDDS composition containing 52.6% (w/v) caprylic/capric

triglycerides as the oil component, 28.2% (w/v) polyoxyl 40 hydrogenated castor oil and 13.1% (w/v) dehydrated alcohol (SEDDS B); b) a SEDDS composition containing 46.0% (w/v) caprylic/capric triglycerides, 28.2% (w/v) caprylocaproyl macrogol 8 glycerides as the surfactant and 19.7% (w/v) dehydrated alcohol (SEDDS C); and c) a corn oil solution. In addition, SEDDS A was also compared to a powder or an aqueous slurry of an amorphous form of the 2,6-di-alkyl-4-silyl-phenol, and an aqueous slurry of the micronized 2,6-di-alkyl-4-silyl-phenol. The amorphous form of 2,6-di-alkyl-4-silyl-phenol was prepared by melting and extrusion of a mixture of 20% crystalline 2,6-di-alkyl-4-silyl-phenol in a water-soluble polymer formulation. The aqueous, micronized slurry of 2,6-di-alkyl-4-silyl-phenol was prepared by bead milling of a crystalline form of the drug in an aqueous formulation. The compositions were administered to rats (150 mg/kg, n=3) and monkeys (90 mg/kg, n=3) in a variety of oral formulations. The micronized slurry was administered at a concentration of 16 mg/mL; the aqueous amorphous slurry was administered at 15 mg/mL; and the amorphous powder at 150 mg/g. Plasma levels of 2,6-di-alkyl-4-silyl-phenol were measured by HPLC, and expressed in terms of $AUC_{0\text{-}25\ hr}$ (the area under the curve from 0 to 25 hr), the C_{max} (maximum plasma concentration) and the T_{max} (time of C_{max}). The data are presented in Table 4.

Table 4. Bioavailability of 2,6-Di-Alkyl-4-Silyl-Phenol Formulations in Rats and Monkeys

Formulation	Rat			Monkey		
	$AUC_{0\text{-}25\ hr}$ (μg.hr/mL)	C_{max} (μg/mL)	T_{max} (hr)	$AUC_{0\text{-}25\ hr}$ (μg.hr/mL)	C_{max} (μg/mL)	T_{max} (hr)
Micronized Slurry	23.1	3.2	5	35.1	2.2	5
Amorphous Slurry[1] or Powder[2]	37.8	5.2	1	10.7	1.1	5
Corn Oil Solution	200.8	20.4	9	48.0	3.3	21
SEDDS A	187.5	18.1	3	164.7	24.6	5
	---	---	---	208.4	28.1	5
SEDDS B	---	---	---	32.0	3.5	7
	---	---	---	30.7	5.1	5
SEDDS C	---	---	---	89.6	8.8	3

[1]The amorphous form of a 2,6-di-alkyl-4-silyl-phenol was made into an aqueous slurry for administration to rats.
[2]The amorphous form of a 2,6-di-alkyl-4-silyl-phenol was diluted with lactose and filled into capsules for administration to monkeys.

The SEDDS composition formulated according to the present invention (SEDDS A) afforded significantly higher bioavailability of the 2,6-di-alkyl-4-silyl-phenol than the other SEDDS compositions in monkeys. SEDDS A produced much higher bioavailability than either the aqueous micronized slurry or the amorphous forms of the 2,6-di-alkyl-4-silyl-phenol in rats and monkeys. Compared with the 2,6-di-alkyl-4-silyl-phenol in corn oil solution, the SEDDS A produced comparable bioavailability in rats and greater bioavailability in monkeys. A corn oil solution is less desirable as a pharmaceutical product due to poor palatability, large volume required and high lipid load delivered.

Surprisingly, it was found that SEDDS A, containing propylene glycol dicaprylate/dicaprate as the oil component, provided a far greater bioavailability of the 2,6-di-alkyl-4-silyl-phenol than a similar SEDDS composition differing only in the substitution of caprylic/capric triglycerides for the oil component (SEDDS B). Both the $AUC_{0\text{-}25\ hr}$ and the C_{max} in monkeys were greater for SEDDS A than for SEDDS B. The substitution of caprylocaproyl macrogol 8 glycerides (SEDDS C) for the polyoxyl 40 hydrogenated castor oil surfactant in SEDDS B slightly increased the $AUC_{0\text{-}25\ hr}$ and the C_{max} values, but not to the levels measured for SEDDS A. The much greater bioavailability of the 2,6-di-alkyl-4-silyl-phenol in SEDDS A compared

to SEDDS B and SEDDS C was unexpected, because propylene glycol dicaprylate/dicaprate differs from the caprylic/capric triglyceride only in substitution of a methyl group for a fatty acid chain present in the triglyceride.

Example 4:

The bioavailability of a 2,6-di-alkyl-4-silyl-phenol in a preferred SEDDS composition of the present invention (Table 1) was compared to that of 2,6-di-alkyl-4-silyl-phenol in another SEDDS of different quantitative composition. The other SEDDS composition comprised a higher concentration 7.5%w/v of 2,6-di-alkyl-4-silyl-phenol, 0.04%w/v butylated hydroxytoluene, 0.10%w/v citric acid anhydrous, 58.31%w/v propylene glycol dicaprylate/dicaprate, 17.17%w/v polyoxyl 40 hydrogenated castor oil, and 10.29% w/w alcohol (SEDDS D). The two formulations were administered to rats at a dose of 150 mg/kg (n = 4). Plasma levels of the 2,6-di-alkyl-4-silyl-phenol were measured by LC/MS/MS, and the bioavailability data are presented in Table 5.

Table 5. Bioavailability of 2,6-Di-Alkyl-4-Silyl-Phenol Formulations in Rats

SEDDS Formulation	Potency (%w/v)	$AUC_{0\text{-}25\ hr}$ (μg•hr/mL)	C_{max} (μg/mL)	T_{max} (hr)
SEDDS A	5.0	331.8	24.2	5
SEDDS D	7.5	244.6	26.0	3

The results show that the changes in potency and quantitative compositions between SEDDS A and SEDDS D did not significantly affect the bioavailability of 2,6-Di-Alkyl-4-Silyl-Phenol.

Various patents and publications are cited herein, and their disclosures are hereby incorporated by reference in their entireties. The present invention is not intended to be limited in scope by the specific embodiments described herein. Although the present invention has been described in detail for the purpose of illustration, various modifications of the invention as disclosed, in addition to those described herein, will become apparent to those of skill in the art from the foregoing description. Such modifications are intended to be encompassed within the scope of the present claims.

CLAIMS

1. A vehicle system for a hydrophobic or lipophilic phenolic antioxidant, comprising:

   a. at least one propylene glycol ester of at least one medium chain fatty acid;

   b. a pharmaceutically acceptable hydrophilic surfactant having an HLB value greater than 10 and being capable of dispersing said oil into water or aqueous media;

   c. a pharmaceutically acceptable non-aqueous protic solvent capable of forming an isotropic mixture with said oil and said surfactant.

2. A vehicle system according to claim 1, wherein said medium chain fatty acid includes at least one member selected from the group consisting of hexanoic, heptanoic, caprylic, pelargonic, capric and lauric acid.

3. A vehicle system according to claim 1 or 2, wherein said hydrophilic surfactant comprises at least one member selected from the group consisting of polyethoxylated long chain saturated fatty acid triglycerides, polyethoxylated long chain unsaturated fatty acid triglycerides, polyethoxylated medium chain saturated fatty acid triglycerides, and polyethoxylated medium chain unsaturated fatty acid triglycerides.

4. A vehicle system according to claim 1 or 2, wherein said hydrophilic surfactant comprises at least one member selected from the group consisting of polyoxyl 40 hydrogenated castor oil, polyoxyl 40 castor oil, polyoxyl 35 castor oil, and caprylocaproyl macrogol-8 glycerides.

5. A vehicle system according to any of the preceding claims, wherein said non-aqueous protic solvent is a mono-, di- or trihydroxy linear aliphatic or aromatic solvent or a combination thereof.

6. A vehicle system according to claim 5, wherein said non-aqueous protic solvent comprises at least one member selected from the group consisting of ethanol, benzyl alcohol, propylene glycol, polyethylene glycol or glycerol.

7. A vehicle system according to any of the preceding claims further comprising a pharmaceutically acceptable chelating agent.

8. A vehicle system according to claim 7, wherein the chelating agent is selected from the group consisting of citric acid, maleic acid, succinic acid, tartaric acid, ethylene diamine tetraacetic acid and ethylene glycol-bis(β-aminoethyl ether) tetraacetic acid.

9. A vehicle system according to any of the preceding claims, further comprising a pharmaceutically acceptable antioxidant.

10. A vehicle system according to claim 9, wherein the antioxidant has an oxidation potential approximately equal or greater than a pharmaceutically active phenolic antioxidant .

11. A vehicle system according to claim 9, wherein said pharmaceutically acceptable antioxidant is a member selected from the group consisting of α-tocopherol, tocopherol acetate, vitamin E polyethylene glycol succinate, propyl gallate, butylated hydroxytoluene and butylated hydroxyanisole.

12. A vehicle system according to claim 1, comprising:
    a. 5-80% weight by volume of said at least one propylene glycol ester;
    b. 5-80% weight by volume of said hydrophilic surfactant;
    c. 5-50% weight by volume of said non-aqueous protic solvent.

13. A vehicle system according to claim 1, comprising:
    a. polyoxyl 40 hydrogenated castor oil at a concentration between 5 and 80% (w/v);
    b. propylene glycol dicaprylate/dicaprate at a concentration between 5 and 80% (w/v);
    c. dehydrated ethanol at a concentration between 5 and 50% (w/v).

14. A pharmaceutical composition comprising:
    a. an effective phenolic antioxidant; and
    b. a vehicle system comprising:
        i. at least one propylene glycol ester of at least one medium chain fatty acid;
        ii. a pharmaceutically acceptable hydrophilic surfactant having an HLB value greater than 10 and being capable of dispersing said oil into water or aqueous media;

iii. a pharmaceutically acceptable non-aqueous protic solvent capable of forming an isotropic mixture with said oil and said surfactant.

15. A pharmaceutical composition according to claim 14 further comprising a pharmaceutically acceptable antioxidant, said antioxidant being soluble in a non-aqueous system.

16. A pharmaceutical composition according to claim 14 or 15 further comprising a pharmaceutically acceptable chelating agent, said chelating agent being soluble in a non-aqueous system

17. A pharmaceutical composition useful in the administration of a hydrophobic or lipophilic drug to a patient in need of such administration, comprising:

a. a hydrophilic surfactant with a hydrophilic-lipophilic balance value greater than 10;

b. one or more medium chain fatty acid esters of propylene glycol; and

c. a non-aqueous protic solvent.

18. A pharmaceutical composition according to claim 17, further comprising one or both of a chelating agent and an antioxidant.

19. A pharmaceutical composition according to claim 17, further comprising at least one chelating agent selected from the group consisting of citric acid, maleic acid, succinic acid, tartaric acid, ethylene diamine tetraacetic acid and ethylene glycol-bis(β-aminoethyl ether) tetraacetic acid.

20. A pharmaceutical composition according to claim 17 or 19, further comprising an antioxidant selected from the group consisting of α-tocopherol, tocopherol acetate, vitamin E polyethylene glycol succinate, propyl gallate, butylated hydroxytoluene and butylated hydroxyanisole.

21. A pharmaceutical composition according to claim 18 or 19, wherein said chelating agent is present in a concentration between 0.01 and 10% (w/v).

22. A pharmaceutical composition according to claim 18 or 20, wherein said antioxidant is present in a concentration between 0.01 and 10% (w/v).

23. A pharmaceutical composition according to claim 17, wherein said hydrophilic surfactant comprises at least one member selected from the group consisting of

polyethoxylated long chain saturated fatty acid triglycerides, polyethoxylated long chain unsaturated fatty acid triglycerides, polyethoxylated medium chain saturated fatty acid triglycerides, and polyethoxylated medium chain unsaturated fatty acid triglycerides.

24. A pharmaceutical composition according to claim 17, wherein said hydrophilic surfactant comprises at least one member selected from the group consisting of polyoxyl 40 hydrogenated castor oil, polyoxyl 40 castor oil, polyoxyl 35 castor oil, and caprylocaproyl macrogol-8 glycerides.

25. A pharmaceutical composition according to claim 17, wherein said medium chain fatty acids comprise at least one member selected from the group consisting of hexanoic acid, heptanoic acid, caprylic acid, pelargonic acid, capric acid and lauric acid.

26. A pharmaceutical composition according to claim 17, wherein said non-aqueous protic solvent comprises a member selected from the group consisting of ethanol, benzyl alcohol, propylene glycol, polyethylene glycol and glycerol.

27. A pharmaceutical composition according to any one of claims 17-24, wherein said hydrophilic surfactant is present at a concentration between 5 and 80% (w/v).

28. A pharmaceutical composition according to claim 17 or 26, wherein said propylene glycol fatty acid ester is present at a concentration between 5 and 80% (w/v).

29. A pharmaceutical composition according to claim 17, wherein said non-aqueous protic solvent is present at a concentration between 5 and 50% (w/v).

30. A pharmaceutical composition according to claim 17, wherein said hydrophilic surfactant is polyoxyl 40 hydrogenated castor oil.

31. A pharmaceutical composition according to claim 17, wherein said propylene glycol fatty acid ester is propylene glycol dicaprylate/dicaprate.

32. A pharmaceutical composition according to claim 17, wherein said non-aqueous solvent is dehydrated ethanol.

33. A pharmaceutical composition according to claim 17, wherein said hydrophilic surfactant is polyoxyl 40 hydrogenated castor oil, said propylene glycol fatty acid ester is propylene glycol dicaprylate/dicaprate, and said non-aqueous solvent is dehydrated ethanol.

34. A pharmaceutical composition according to claim 17, wherein said hydrophilic surfactant is polyoxyl 40 hydrogenated castor oil at a concentration between 5 and 80% (w/v).

35. A pharmaceutical composition according to claim 17, wherein said propylene glycol fatty acid ester is propylene glycol dicaprylate/dicaprate at a concentration between 5 and 80% (w/v).

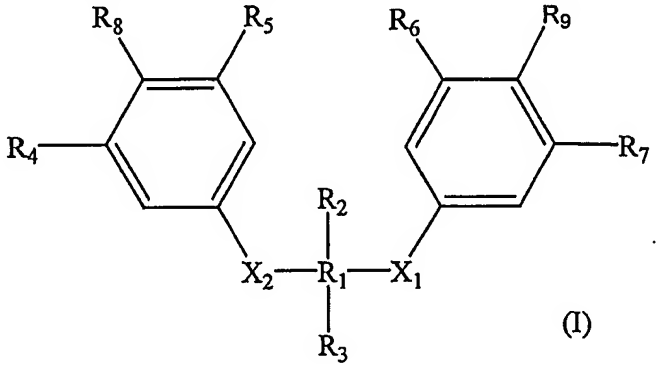
36. A pharmaceutical composition according to claim 17, wherein said non-aqueous protic solvent is dehydrated ethanol at a concentration between 5 and 50% (w/v).

37. A pharmaceutical composition according to claim 17, wherein said hydrophilic surfactant is polyoxyl 40 hydrogenated castor oil at a concentration between 5 and 80% (w/v), said propylene glycol fatty acid ester is propylene glycol dicaprylate/dicaprate at a concentration between 5 and 80% (w/v), and said non-aqueous solvent is dehydrated ethanol at a concentration between 5 and 50% (w/v).

38. A pharmaceutical composition according to claim 17, further comprising a pharmaceutically acceptable antioxidant.

39. A pharmaceutical composition according to claim 38, wherein said antioxidant is a phenolic antioxidant.

40. A pharmaceutical composition according to claim 38, wherein said antioxidant is a phenolic antioxidant having the general formula



(I)

wherein:

X_1 and X_2 are independently selected from the group consisting of oxy and a dialkyl substituted silyl;

R_1 is C_1-C_4 alkyl;

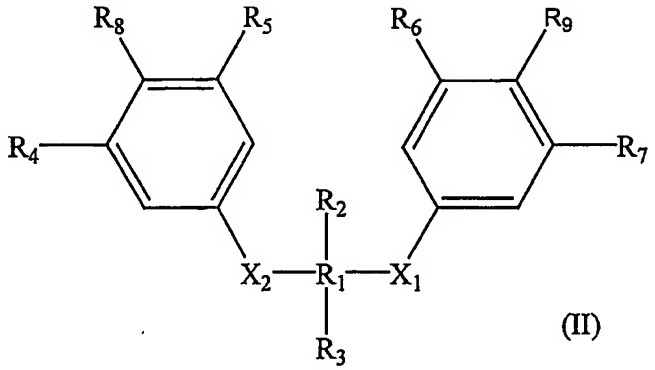
R_2 and R_3 are independently selected from the group consisting of H and a C_1-C_4 alkyl;

R_4, R_5, R_6, and R_7 are independently selected from the group consisting of H, methoxy, and a branched or straight chain C_1-C_6 alkyl; and

R_8 and R_9 are independently selected from the group consisting of hydrogen, hydroxy, trifluoromethyl, halide, amine, alkyl, alkenyl, aryl, heteroaryl, alkanoyl, aryloyl, heteroaryloyl, -O(C_1-C_6 alkyl), –OCO-(H or C_1-C_7 alkyl), –OCO-(C_3-C_7 alkenyl), –OCO-(aryl), -OCO-(heteroaryl), –(C_0-C_8 alkyl)-COOH, –(C_2-C_8 alkenyl)-COOH, –OCO-(C_0-C_6 alkyl)-COOH, –OCO-(C_2-C_6 alkenyl)-COOH, –CO-(C_0-C_6 alkyl)-COOH, and –CO-(C_2-C_6 alkenyl)-COOH;

wherein when the R_8 or R_9 substituents are alkyl, alkenyl, aryl, heteroaryl, alkanoyl, aryloyl, heteroaryloyl, –O(C_1-C_6 alkyl), –OCO-(H or C_1-C_7 alkyl), –OCO-(C_3-C_7 alkenyl), –OCO-(aryl), –OCO-(heteroaryl), –(C_0-C_8 alkyl)-COOH, –(C_2-C_8 alkenyl)-COOH, –OCO-(C_0-C_6 alkyl)-COOH, –OCO-(C_2-C_6 alkenyl)-COOH, –CO-(C_0-C_6 alkyl)-COOH, or –CO-(C_2-C_6 alkenyl)-COOH, they may be independently substituted with one or more functionalities independently selected from the group consisting of C_1-C_6 alkyl, halogen, –OH, $–OCH_3$, $–OCH_2CH_3$, halomethyl, dihalomethyl, trihalomethyl, $–NH_2$, $–NO_2$, –CN, –NC, –C(=NH)(-NH_2), –SH, –COOH, $–COOCH_3$, and $–COOCH_2CH_3$.

41. A pharmaceutical composition according to claim 38, wherein said antioxidant is a phenolic antioxidant having the general formula



(II)

wherein

X_1 and X_2 are independently selected from the group consisting of thio, oxy, and a dialkyl substituted silyl;

R_1 is C_1-C_4 alkyl;

R_2 and R_3 are independently selected from the group consisting of H and a C_1-C_4 alkyl;

R_4, R_5, R_6, and R_7 are independently selected from the group consisting of H, methoxy, and a branched or straight chain C_1-C_6 alkyl; and

R_8 and R_9 are independently selected from the group consisting of hydrogen, hydroxy, trifluoromethyl, halide, amine, alkyl, alkenyl, aryl, heteroaryl, alkanoyl, aryloyl, heteroaryloyl, –O(C_1-C_6 alkyl), –OCO-(H or C_1-C_7 alkyl), –OCO-(C_3-C_7 alkenyl), –OCO-(aryl), –OCO-(heteroaryl), –(C_0-C_8 alkyl)-COOH, –(C_2-C_8 alkenyl)-COOH, –OCO-(C_0-C_6 alkyl)-COOH,
–OCO-(C_2-C_6 alkenyl)-COOH, –CO-(C_0-C_6 alkyl)-COOH, and –CO-(C_2-C_6 alkenyl)-COOH;
wherein when the R_8 or R_9 substituents are alkyl, alkenyl, aryl, heteroaryl, alkanoyl, aryloyl, heteroaryloyl, –O(C_1-C_6 alkyl), –OCO-(H or C_1-C_7 alkyl), –OCO-(C_3-C_7 alkenyl), –OCO-(aryl), –OCO-(heteroaryl), –(C_0-C_8 alkyl)-COOH, –(C_2-C_8 alkenyl)-COOH, –OCO-(C_0-C_6 alkyl)-COOH, –OCO-(C_2-C_6 alkenyl)-COOH, –CO-(C_0-C_6 alkyl)-COOH, or –CO-(C_2-C_6 alkenyl)-COOH, they may be independently substituted with one or more functionalities independently selected from the group consisting of C_1-C_6 alkyl, halogen, –OH, –OCH_3, –OCH_2CH_3, halomethyl, dihalomethyl, trihalomethyl, –NH_2, –NO_2, –CN, –NC, –C(=NH)(-NH_2), –SH, –COOH, –$COOCH_3$, and –$COOCH_2CH_3$.

42. A pharmaceutical composition according to any one of claims 38-41, wherein said antioxidant is present at a concentration between 0.1 and 50% (w/v).

43. A pharmaceutical composition according to any one of claims 38-41, wherein said hydrophilic surfactant is polyoxyl 40 hydrogenated castor oil, said propylene glycol fatty acid ester is propylene glycol dicaprylate/dicaprate, and said non-aqueous solvent is dehydrated ethanol.

44. A pharmaceutical composition according to claim 38, wherein said hydrophilic surfactant is polyoxyl 40 hydrogenated castor oil that is present at a concentration

between 5 and 80% (w/v), said propylene glycol fatty acid ester is propylene glycol dicaprylate/dicaprate that is present at a concentration between 5 and 80% (w/v), and said non-aqueous solvent is dehydrated ethanol that is present at a concentration between 5 and 50% (w/v).

45. A pharmaceutical composition useful in the administration of a hydrophobic or lipophilic drug to a patient in need of such administration, wherein the pharmaceutical composition comprises polyoxyl 40 hydrogenated castor oil at a concentration between 5 and 80% (w/v); propylene glycol dicaprylate/dicaprate at a concentration between 5 and 80% (w/v); dehydrated ethanol at a concentration between 5 and 50% (w/v).

46. The pharmaceutical composition of claim 45, further comprising butylated hydroxytoluene at a concentration of between 0.01 and 10% (w/v).

47. The pharmaceutical composition of claim 45, further comprising citric acid at a concentration between 0.01 and 10% (w/v).

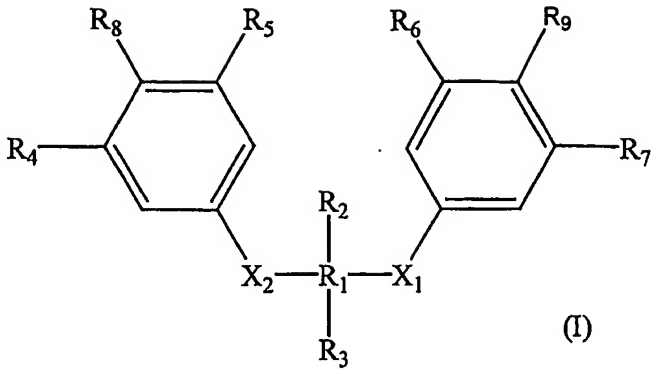
48. A pharmaceutical composition useful in the administration of a hydrophobic or lipophilic drug to a patient in need of such administration, comprising polyoxyl 40 hydrogenated castor oil at a concentration between 5 and 80% (w/v); propylene glycol dicaprylate/dicaprate at a concentration between 5 and 80% (w/v); dehydrated ethanol at a concentration between 5 and 50% (w/v).

49. The pharmaceutical composition of claim 48, further comprising butylated hydroxytoluene at a concentration of between 0.01 and 10% (w/v).

50. The pharmaceutical composition of claim 48, further comprising citric acid at a concentration between 0.01 and 10% (w/v).

51. A method for treating a patient in need of a vascular protective treatment, comprising administering to said patient an amount effective to provide vascular protection of a phenolic antioxidant in a pharmaceutically acceptable carrier, wherein said carrier comprises a hydrophilic surfactant with a hydrophilic-lipophilic balance value greater than 10; a propylene glycol fatty acid ester that is one or more medium chain fatty acid esters of propylene glycol; and a non-aqueous protic solvent.

52. The method of claim 51, wherein said phenolic antioxidant has the general formula



(I)

wherein:

X_1 and X_2 are independently selected from the group consisting of oxy and a dialkyl substituted silyl;

R_1 is C_1-C_4 alkyl;

R_2 and R_3 are independently selected from the group consisting of H and a C_1-C_4 alkyl;

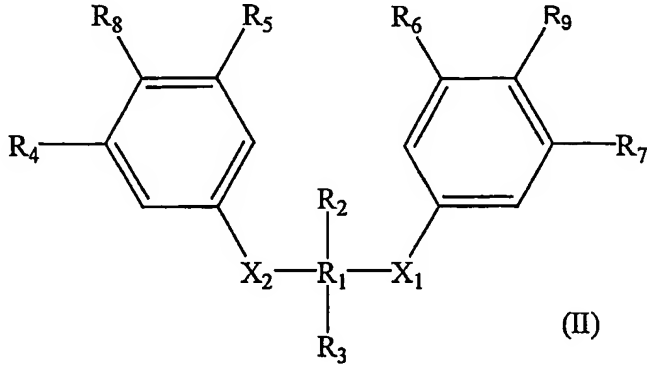
R_4, R_5, R_6, and R_7 are independently selected from the group consisting of H, methoxy, and a branched or straight chain C_1-C_6 alkyl; and

R_8 and R_9 are independently selected from the group consisting of hydrogen, hydroxy, trifluoromethyl, halide, amine, alkyl, alkenyl, aryl, heteroaryl, alkanoyl, aryloyl, heteroaryloyl, –O(C_1-C_6 alkyl), –OCO-(H or C_1-C_7 alkyl), –OCO-(C_3-C_7 alkenyl), –OCO-(aryl), –OCO-(heteroaryl), –(C_0-C_8 alkyl)-COOH, –(C_2-C_8 alkenyl)-COOH, –OCO-(C_0-C_6 alkyl)-COOH,
–OCO-(C_2-C_6 alkenyl)-COOH, –CO-(C_0-C_6 alkyl)-COOH, and –CO-(C_2-C_6 alkenyl)-COOH;

wherein when the R_8 or R_9 substituents are alkyl, alkenyl, aryl, heteroaryl, alkanoyl, aryloyl, heteroaryloyl, –O(C_1-C_6 alkyl), –OCO-(H or C_1-C_7 alkyl), –OCO-(C_3-C_7 alkenyl),
–OCO-(aryl), –OCO-(heteroaryl), –(C_0-C_8 alkyl)-COOH, –(C_2-C_8 alkenyl)-COOH, –OCO-(C_0-C_6 alkyl)-COOH, –OCO-(C_2-C_6 alkenyl)-COOH, –CO-(C_0-C_6 alkyl)-COOH, or –CO-(C_2-C_6 alkenyl)-COOH, they may be independently substituted with one or more functionalities independently selected from the group consisting of C_1-C_6 alkyl, halogen,

–OH, –OCH_3, –OCH_2CH_3, halomethyl, dihalomethyl, trihalomethyl, –NH_2, –NO_2, –CN, –NC, –C(=NH)(-NH_2), –SH, –COOH, –$COOCH_3$, and –$COOCH_2CH_3$.

53. The method of claim 51, wherein said phenolic antioxidant has the general formula



(II)

wherein

X_1 and X_2 are independently selected from the group consisting of thio, oxy, and a dialkyl substituted silyl;

R_1 is C_1-C_4 alkyl;

R_2 and R_3 are independently selected from the group consisting of H and a C_1-C_4 alkyl;

R_4, R_5, R_6, and R_7 are independently selected from the group consisting of H, methoxy, and a branched or straight chain C_1-C_6 alkyl; and

R_8 and R_9 are independently selected from the group consisting of hydrogen, hydroxy, trifluoromethyl, halide, amine, alkyl, alkenyl, aryl, heteroaryl, alkanoyl, aryloyl, heteroaryloyl, –O(C_1-C_6 alkyl), –OCO-(H or C_1-C_7 alkyl), –OCO-(C_3-C_7 alkenyl), –OCO-(aryl), –OCO-(heteroaryl), –(C_0-C_8 alkyl)-COOH, –(C_2-C_8 alkenyl)-COOH, –OCO-(C_0-C_6 alkyl)-COOH, –OCO-(C_2-C_6 alkenyl)-COOH, –CO-(C_0-C_6 alkyl)-COOH, and –CO-(C_2-C_6 alkenyl)-COOH;

wherein when the R_8 or R_9 substituents are alkyl, alkenyl, aryl, heteroaryl, alkanoyl, aryloyl, heteroaryloyl, –O(C_1-C_6 alkyl), –OCO-(H or C_1-C_7 alkyl), –OCO-(C_3-C_7 alkenyl), –OCO-(aryl), –OCO-(heteroaryl), –(C_0-C_8 alkyl)-COOH, –(C_2-C_8 alkenyl)-COOH, –OCO-(C_0-C_6 alkyl)-COOH, –OCO-(C_2-C_6 alkenyl)-COOH, –CO-(C_0-C_6 alkyl)-COOH, or –CO-(C_2-C_6 alkenyl)-COOH, they may be independently substituted with one

or more functionalities independently selected from the group consisting of C_1-C_6 alkyl, halogen, –OH, $–OCH_3$, $–OCH_2CH_3$, halomethyl, dihalomethyl, trihalomethyl, $–NH_2$, $–NO_2$, –CN, –NC, $–C(=NH)(-NH_2)$, –SH, –COOH, $–COOCH_3$, and $–COOCH_2CH_3$.

54. The method of any one of claims 51 to 53, wherein said phenolic antioxidant is present at a concentration between 0.1 and 50% (w/v).

55. The method of any one of claims 51 to 54, wherein said hydrophilic surfactant is polyoxyl 40 hydrogenated castor oil, said propylene glycol fatty acid ester is propylene glycol dicaprylate/dicaprate, and said non-aqueous solvent is dehydrated ethanol.

56. The method of any one of claims 51 to 54, wherein said hydrophilic surfactant is polyoxyl 40 hydrogenated castor oil that is present at a concentration between 5 and 80% (w/v), said propylene glycol fatty acid ester is propylene glycol dicaprylate/dicaprate at a concentration between 5 and 80% (w/v), and said non-aqueous solvent is dehydrated ethanol that is present at a concentration between 5 and 50% (w/v).

57. The method of claim 51, further comprising one or both of a chelating agent and an antioxidant.

58. The method of any one of claims 51 to 56, further comprising a chelating agent selected from the group consisting of citric acid, maleic acid, succinic acid, tartaric acid, ethylene diamine tetraacetic acid and ethylene glycol-bis(β-aminoethyl ether) tetraacetic acid.

59. The method of claim 51, further comprising an antioxidant selected from the group consisting of α-tocopherol, tocopherol acetate, vitamin E polyethylene glycol succinate, propyl gallate, butylated hydroxytoluene and butylated hydroxyanisole.

60. The method of claim 57, wherein said chelating agent is present in a concentration between 0.01 and 10% (w/v).

61. The method of claim 57, wherein said antioxidant is present in a concentration between 0.01 and 10% (w/v).

62. The method of any one of claims 51 to 54, wherein said hydrophilic surfactant is a member selected from the group consisting of polyethoxylated long chain saturated fatty acid triglycerides, polyethoxylated long chain unsaturated fatty acid triglycerides,

polyethoxylated medium chain saturated fatty acid triglycerides, and polyethoxylated medium chain unsaturated fatty acid triglycerides.

63. The method of any of claims 51 to 54 , wherein said hydrophilic surfactant is a member selected from the group consisting of polyoxyl 40 hydrogenated castor oil, polyoxyl 40 castor oil, polyoxyl 35 castor oil, and caprylocaproyl macrogol-8 glycerides.

64. The method of any of claims 51 to 54, wherein said propylene glycol fatty acid ester includes one or more members selected from the group consisting of propylene glycol dicaprylate/dicaprate, propylene glycol dipelargonate, and propylene glycol dilaurate.

65. The method of any of claims 51 to 54, wherein said non-aqueous protic solvent is a member selected from the group consisting of ethanol, benzyl alcohol, propylene glycol, polyethylene glycol and glycerol.

66. The method of any of claims 51 to 54, wherein said hydrophilic surfactant is present at a concentration between 5 and 80% (w/v).

67. The method of any of claims-51 to 54, wherein said propylene glycol fatty acid ester is present at a concentration between 5 and 80% (w/v).

68. The method of any of claims 51 to 54, wherein said non-aqueous protic solvent is present at a concentration between 5 and 50% (w/v).

69. The method of any of claims 51 to 54, wherein said hydrophilic surfactant is polyoxyl 40 hydrogenated castor oil.

70. The method of any of claims 51 to 54, wherein said propylene glycol fatty acid ester is propylene glycol dicaprylate/dicaprate.

71. The method of any of claims 51 to 54, wherein said non-aqueous solvent is dehydrated ethanol.

72. The method of any of claims 51 to 54, wherein said hydrophilic surfactant is polyoxyl 40 hydrogenated castor oil at a concentration between 5 and 80% (w/v).

73. The method of any of claims 51 to 54, wherein said propylene glycol fatty acid ester is propylene glycol dicaprylate/dicaprate at a concentration between 5 and 80% (w/v).

74. The method of any of claims 51 to 54, wherein said non-aqueous protic solvent is dehydrated ethanol at a concentration between 5 and 50% (w/v).

75. The method of any of claims 51 to 54, wherein said hydrophilic surfactant is polyoxyl 40 hydrogenated castor oil at a concentration between 5 and 80% (w/v), said propylene glycol fatty acid ester is propylene glycol dicaprylate/dicaprate that is present at a concentration between 5 and 80% (w/v), and said non-aqueous solvent is dehydrated ethanol at a concentration between 5 and 50% (w/v).

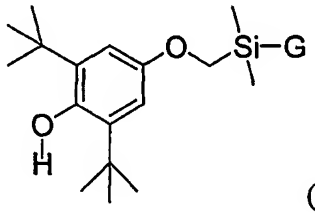
76. A method for treating a patient in need of a vascular protective treatment, comprising administering to said patient an amount effective to provide vascular protection of a phenolic antioxidant in a pharmaceutically acceptable carrier comprising polyoxyl 40 hydrogenated castor oil at a concentration between 5 and 80% (w/v); propylene glycol dicaprylate/dicaprate at a concentration between 5 and 80% (w/v); dehydrated ethanol at a concentration between 5 and 50% (w/v).

77. The method of claim 76, wherein the pharmaceutically acceptable carrier further comprises butylated hydroxytoluene at a concentration of between 0.01 and 10% (w/v).

78. The method of claim 76, wherein the pharmaceutically acceptable carrier further comprises citric acid at a concentration between 0.01 and 10% (w/v).

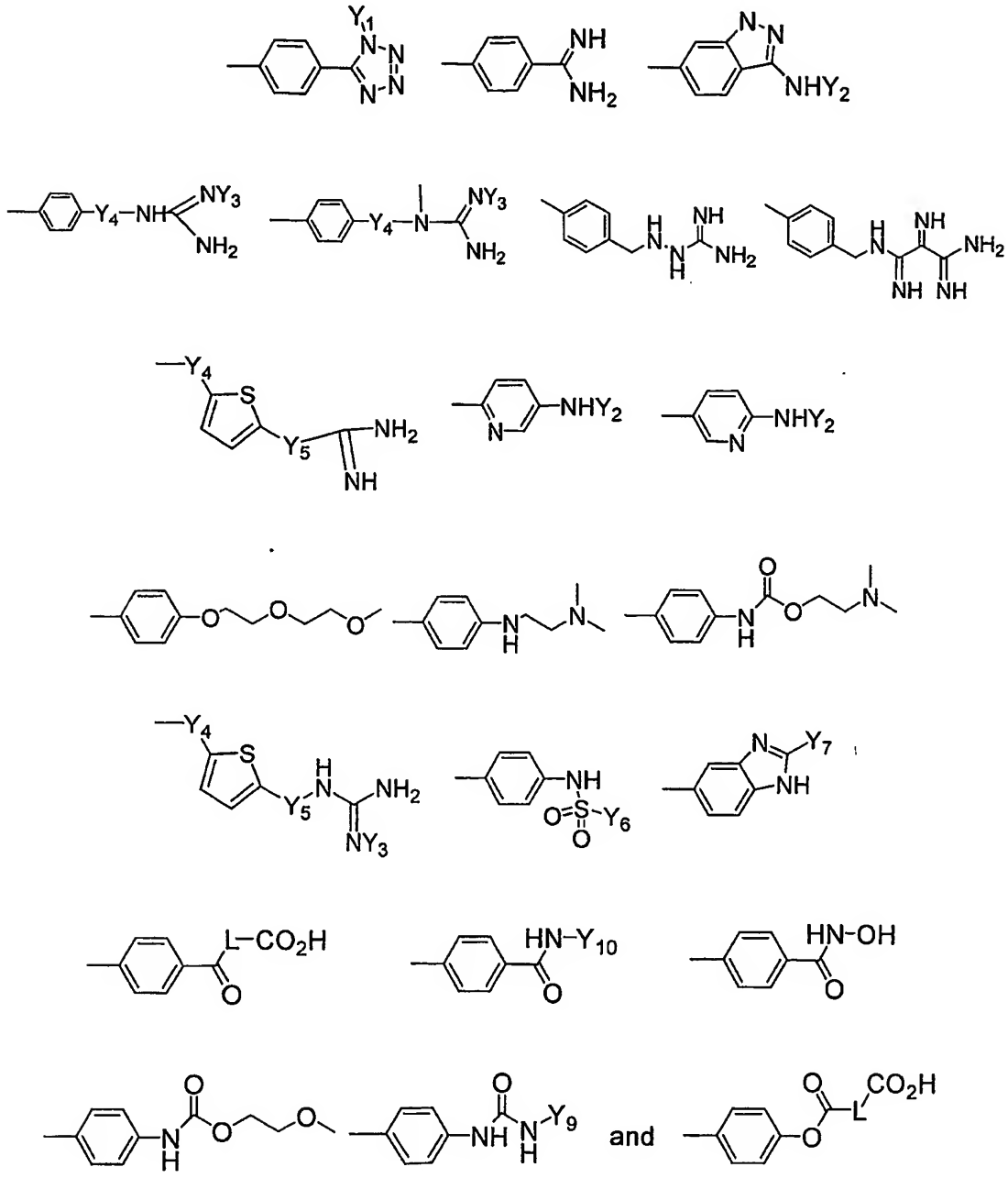
79. The method of claim 76, wherein said phenolic antioxidant is present at a concentration between 0.1 and 50% (w/v).

80. A pharmaceutical composition according to claim 38, wherein said antioxidant is a compound of Formula (V):



(V)

wherein G is selected from the group consisting of:



wherein:

Y_1 is –H, C_1-C_4 alkyl, or C_3-C_6 alkenyl;

Y_2 is –H, C_1-C_4 alkyl, or C_3-C_6 alkenyl, aryl, heteroaryl, aryloyl, alkanoyl, or heteroaryloyl;

Y_3 is –H, –CN, C_1-C_4 alkyl, C_3-C_6 alkenyl, aryl or heteroaryl;

Y_4 is $(CH_2)_n$, where n is 0-4, or C_2-C_6 alkenyl;

Y_5 is NH, $(CH_2)_n$, where n is 0-4, or C_2-C_6 alkenyl;

Y_6 is C_1-C_4 alkyl, C_3-C_6 alkenyl, aryl, heteroaryl, alkylaryl, or alkylheteroaryl;

Y_7 is H, C_1-C_4 alkyl, C_3-C_6 alkenyl, aryl, heteroaryl, alkylaryl, or alkylheteroaryl, or NH Y_8;

Y_8 is C_1-C_4 alkyl, C_3-C_6 alkenyl, aryl, heteroaryl, alkylaryl, or alkylheteroaryl;

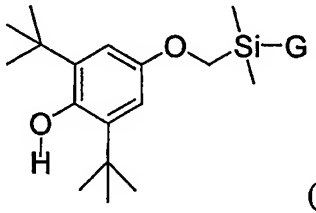
Y_9 is C_1-C_4 alkyl, C_3-C_6 alkenyl, aryl, or heteroaryl;

Y_{10} is alkyl, aryl, heteroaryl, alkylaryl, or alkylheteroaryl;

L is C_1-C_6 alkyl or C_2-C_6 alkenyl; and

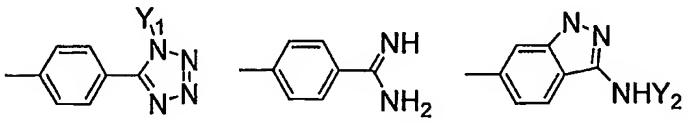
wherein G may be additionally substituted with one or more substituents independently selected from the group consisting of –F, –Cl, –Br, –I, $–NH_2$, –OH, –CN, –SH, $–CH_3$, $–CH_2CH_3$, $–CF_3$, $–OCH_3$, $–OCH_2CH_3$, –COOH, $–COOCH_3$, and $–COOCH_2CH_3$.

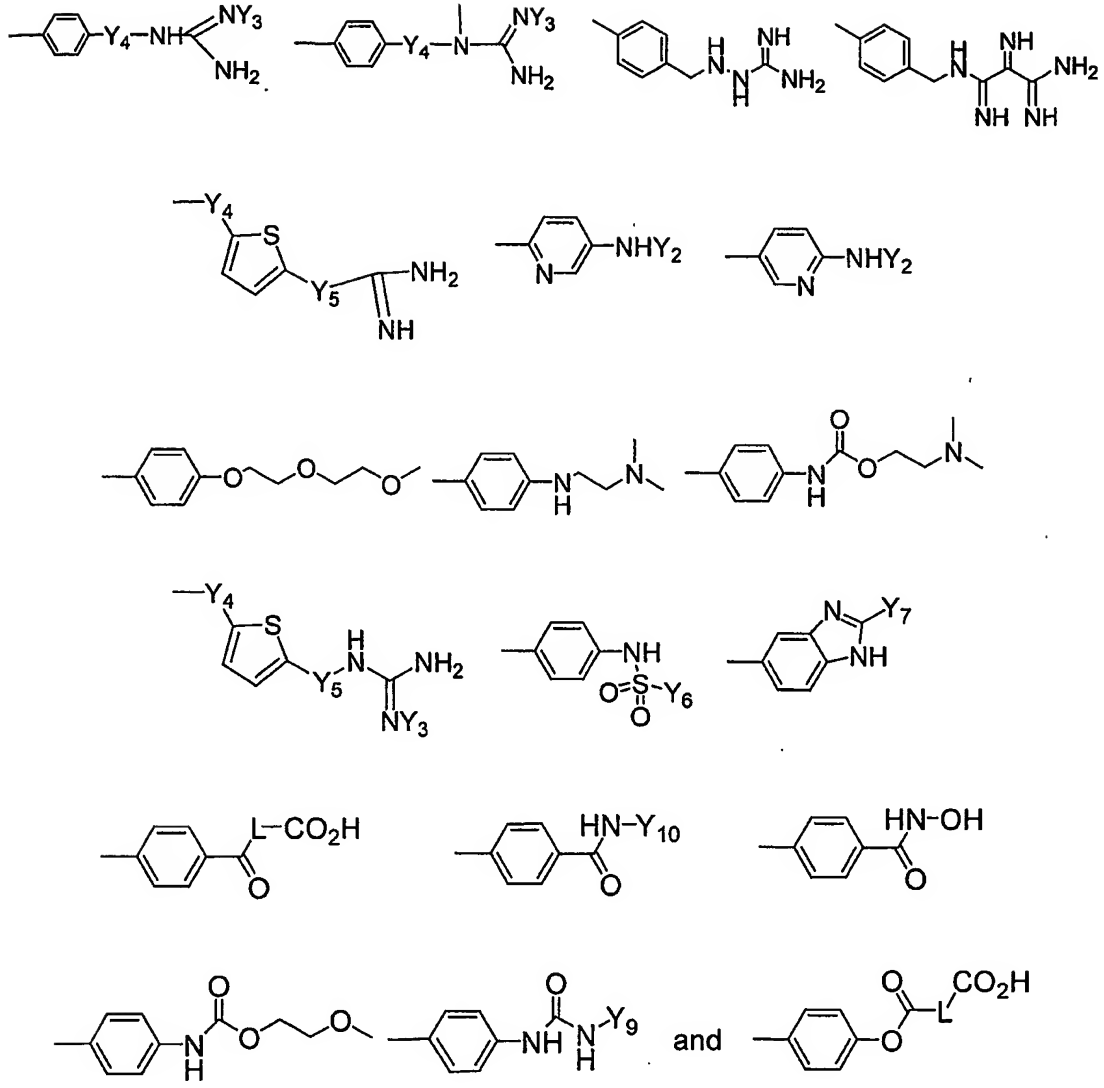
81. The method of claim 51, wherein said antioxidant is a compound of Formula (V):



(V)

wherein G is selected from the group consisting of:





wherein:

Y_1 is –H, C_1-C_4 alkyl, or C_3-C_6 alkenyl;

Y_2 is –H, C_1-C_4 alkyl, or C_3-C_6 alkenyl, aryl, heteroaryl, aryloyl, alkanoyl, or heteroaryloyl;

Y_3 is –H, –CN, C_1-C_4 alkyl, C_3-C_6 alkenyl, aryl or heteroaryl;

Y_4 is $(CH_2)_n$, where n is 0-4, or C_2-C_6 alkenyl;

Y_5 is NH, $(CH_2)_n$, where n is 0-4, or C_2-C_6 alkenyl;

Y_6 is C_1-C_4 alkyl, C_3-C_6 alkenyl, aryl, heteroaryl, alkylaryl, or alkylheteroaryl;

Y_7 is H, C_1-C_4 alkyl, C_3-C_6 alkenyl, aryl, heteroaryl, alkylaryl, or alkylheteroaryl, or NH Y_8;

Y_8 is C_1-C_4 alkyl, C_3-C_6 alkenyl, aryl, heteroaryl, alkylaryl, or alkylheteroaryl;

Y_9 is C_1-C_4 alkyl, C_3-C_6 alkenyl, aryl, or heteroaryl;

Y_{10} is alkyl, aryl, heteroaryl, alkylaryl, or alkylheteroaryl;

L is C_1-C_6 alkyl or C_2-C_6 alkenyl; and

wherein G may be additionally substituted with one or more substituents independently selected from the group consisting of –F, –Cl, –Br, –I, $–NH_2$, –OH, –CN, –SH, $–CH_3$, $–CH_2CH_3$, $–CF_3$, $–OCH_3$, $–OCH_2CH_3$, –COOH, $–COOCH_3$, and – $COOCH_2CH_3$.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2004/034265

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/107 A61K31/695 A61K31/085 A61K31/09 A61K31/095
A61P9/00 A61P9/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99/29300 A (MISHRA AWADHESH K ; PARIKH INDU (CA); MOUSSA ISKANDAR (CA); RTP PHARMA) 17 June 1999 (1999-06-17) page 6, last paragraph page 13 - page 16; examples 4,5,8-11	1-81
X	WO 99/49848 A (RTP PHARMA INC) 7 October 1999 (1999-10-07) page 8 - page 9; examples 1,3,4	1-81
X	EP 1 151 755 A (PANACEA BIOTEC LTD) 7 November 2001 (2001-11-07) paragraphs '0033!, '0040!	1-81
X	FR 2 710 535 A (GATTEFOSSE ETS SA) 7 April 1995 (1995-04-07) page 8; example 1	1-81

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 February 2005	18/02/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Büttner, U

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Form PCT/ISA/210 (second sheet) (January 2004)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00/33862 A (PHARMASOLUTIONS INC) 15 June 2000 (2000-06-15) page 9, paragraph 2 page 11, paragraph 3 page 19, last paragraph page 23, paragraph 1-3 page 25, paragraph 3	1-81
X	EP 1 205 180 A (R.P. SCHERER TECHNOLOGIES, INC) 15 May 2002 (2002-05-15) page 7, paragraph 48 page 11, line 27 page 12, paragraph 38	1-81
A	WO 92/10996 A1 (MERRELL DOW PHARMACEUTICALS INC) 9 July 1992 (1992-07-09) page 2, line 20 - line 35 page 5, line 21 page 6; table 2	1-81
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A	US 5 155 250 A (MAO SIMON J T ET AL) 13 October 1992 (1992-10-13) cited in the application column 10	1-81

INTERNATIONAL SEARCH REPORT

national application No.
PCT/US2004/034265

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: –
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 51-79 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

information on patent family members

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